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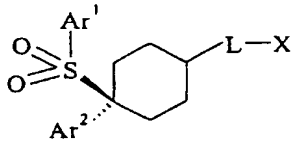
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(54) Title: CYCLOHEXYL SULPHONE DERIVATIVES AS GAMMA-SECRETASE INHIBITORS



(I)

(57) Abstract: Compounds of formula (I) inhibit the processing of APP by gamma-secretase, and hence are useful in treatment of Alzheimer's disease.

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WO 2004/031137 A1

CYCLOHEXYL SULPHONE DERIVATIVES AS GAMMA-SECRETASE INHIBITORS

The present invention relates to a novel class of compounds, their salts, pharmaceutical compositions comprising them, processes for making them and their use in therapy of the human body. In particular, the invention relates to novel cyclohexyl sulphones which inhibit the processing of APP by γ-secretase, and hence are useful in the treatment or prevention of Alzheimer's disease.

Alzheimer's disease (AD) is the most prevalent form of dementia. Although primarily a disease of the elderly, affecting up to 10% of the population over the age of 65, AD also affects significant numbers of younger patients with a genetic predisposition. It is a neurodegenerative disorder, clinically characterized by progressive loss of memory and cognitive function, and pathologically characterized by the deposition of extracellular proteinaceous plaques in the cortical and associative brain regions of sufferers. These plaques mainly comprise fibrillar aggregates of β-amyloid peptide (Aβ). The role of secretases, including the putative γ-secretase, in the processing of amyloid precursor protein (APP) to form Aβ is well documented in the literature and is reviewed, for example, in WO 01/70677.

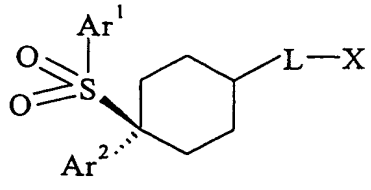
There are relatively few reports in the literature of compounds with inhibitory activity towards γ-secretase, as measured in cell-based assays. These are reviewed in WO 01/70677. Many of the relevant compounds are peptides or peptide derivatives.

WO 00/50391 discloses a broad class of sulphonamides as modulators of the production of β-amyloid, but neither discloses nor suggests the compounds of the present invention.

The present invention provides a novel class of cyclohexyl sulphones which are useful in the treatment or prevention of AD by inhibiting the

processing of APP by the putative γ-secretase, thus arresting the production of Aβ.

According to the invention, there is provided a compound of formula I:



I

wherein

X represents SCN, SR^1, $S(O)R^1$, $(CR^aR^b)_mSO_2R^1$, $SO_2N(R^2)_2$, SO_2NHCOR^1, $SO_2NHN(R^2)_2$, $OSO_2N(R^2)_2$, $OS(O)N(R^2)_2$, OSO_2NHCOR^1, COR^4, $NHCOR^1$, $NHCO_2R^1$, $NHCON(R^2)_2$, $NHSO_2R^1$ or $NHSO_2N(R^2)_2$;

m is 0 or 1

R^a represents H or C_{1-4}alkyl;

R^b represents H, C_{1-4}alkyl, CO_2H, C_{1-4}alkoxycarbonyl or C_{1-4}alkylsulphonyl; or R^b may combine with R^1 to form a 5- or 6-membered ring;

L represents a bond, =CH- or $-(CHR^a)_n-$; with the proviso that L does not represent a bond when X represents $NHCOR^1$, $NHCO_2R^1$ or $NHSO_2R^1$; and with the proviso that if L represents =CH-, X represents SO_2R^1 or COR^4;

n is 1, 2 or 3;

R^1 represents CF_3 or C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-9}cycloalkyl or C_{3-6}cycloalkylC_{1-6}alkyl, any of which may bear up to 2 substituents selected from halogen, CN, CF_3, OR^3, COR^3, CO_2R^3, $OCOR^{3a}$, SO_2R^{3a}, $N(R^5)_2$, and $CON(R^5)_2$,

or R^1 represents aryl, arylC_{1-6}alkyl, C-heterocyclyl or C-heterocyclylC_{1-6}alkyl;

or R^1 may combine with R^b to form a 5- or 6-membered ring;

each R^2 independently represents H, C_{1-6}alkoxy, or C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-9}cycloalkyl or C_{3-6}cycloalkylC_{1-6}alkyl, any of which may bear up to 2 substituents selected from halogen, CN, CF_3, OR^3, COR^3, CO_2R^3, $OCOR^{3a}$, and $CON(R^5)_2$; or aryl, arylC_{1-6}alkyl, C-heterocyclyl or C-heterocyclylC_{1-6}alkyl;

or two R^2 groups together with a nitrogen atom to which they are mutually attached complete an N-heterocyclyl group;

R^3 represents H, C_{1-4}alkyl, phenyl or heteroaryl;

R^{3a} represents C_{1-4}alkyl, phenyl or heteroaryl;

R^4 represents $(CR^aR^b)SO_2R^1$, pyridine N-oxide, or phenyl or heteroaryl which bear a substituent selected from CO_2H, methylenedioxy, difluoromethylenedioxy, COR^3, C-heterocyclyl, C_{1-4}alkylsulphonyl and substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, OR^3, CO_2R^3, $OCOR^{3a}$, $N(R^5)_2$ and $CON(R^5)_2$;

R^5 represents H or C_{1-4}alkyl, or two R^5 groups together with a nitrogen atom to which they are mutually attached complete an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine or thiomorpholine-1,1-dioxide ring;

Ar^1 and Ar^2 independently represent phenyl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, CHF_2, OH, OCF_3, CHO, CH=NOH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, C_{2-6}acyl, C_{2-6}alkenyl and C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

"aryl" at every occurrence thereof refers to phenyl or heteroaryl which optionally bear up to 3 substituents selected from halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^{3a}$, $N(R^5)_2$, $CON(R^5)_2$ and optionally-substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, phenyl, OR^3, CO_2R^3, $OCOR^{3a}$, $N(R^5)_2$ and $CON(R^5)_2$; and

"C-heterocyclyl" and "N-heterocyclyl" at every occurrence thereof refer respectively to a heterocyclic ring system bonded through carbon or nitrogen, said ring system being non-aromatic and comprising up to 10 atoms, at least one of which is O, N or S, and optionally bearing up to 3 substituents selected from oxo, halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^{3a}$, OSO_2R^{3a}, $N(R^5)_2$, $CON(R^5)_2$ and optionally-substituted phenyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, OR^3, CO_2R^3, $OCOR^{3a}$, $N(R^5)_2$ and $CON(R^5)_2$;

or a pharmaceutically acceptable salt thereof.

Where a variable occurs more than once in formula I, the individual occurrences are independent of each other, unless otherwise indicated.

As used herein, the expression "C_{1-x}alkyl" where x is an integer greater than 1 refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C_{2-6}alkenyl", "hydroxyC_{1-6}alkyl", "heteroarylC_{1-6}alkyl", "C_{2-6}alkynyl" and "C_{1-6}alkoxy" are to be construed in an analogous manner.

The expression "C_{3-9}cycloalkyl" as used herein refers to nonaromatic monocyclic or fused bicyclic hydrocarbon ring systems comprising from 3 to 9 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl and bicyclo[2.2.1]heptyl. Monocyclic systems of 3 to 6 members are preferred.

The expression "C_{3-6} cycloalkylC_{1-6}alkyl" as used herein includes cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

The expression "C_{2-6}acyl" as used herein refers to C_{1-5}alkylcarbonyl groups in which the alkyl portion may be straight chain, branched or cyclic, and may be halogenated. Examples include acetyl, propionyl and trifluoroacetyl.

The expression "heterocyclyl" as defined herein includes both monocyclic and fused bicyclic systems of up to 10 ring atoms selected from C, N, O and S. Mono- or bicyclic systems of up to 7 ring atoms are preferred, and monocyclic systems of 4, 5 or 6 ring atoms are most preferred. Examples of heterocyclic ring systems include azetidinyl, pyrrolidinyl, 3-pyrrolinyl, terahydrofuryl, 1,3-dioxolanyl, tetrahydrothiophenyl, tetrahydropyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, 2,5-diazabicyclo[2.2.1]heptyl, 2-aza-5-oxabicyclo[2.2.1]heptyl and 1,4-dioxa-8-azaspiro[4.5]decanyl. Unless otherwise indicated, heterocyclyl groups may be bonded through a ring carbon atom or a ring nitrogen atom where present. "C-heterocyclyl" indicates bonding through carbon, while "N-heterocyclyl" indicates bonding through nitrogen.

The expression "heteroaryl" as used herein means a monocyclic system of 5 or 6 ring atoms, or fused bicyclic system of up to 10 ring atoms, selected from C, N, O and S, wherein at least one of the constituent rings is aromatic and comprises at least one ring atom which is other than carbon. Monocyclic systems of 5 or 6 members are preferred. Examples of heteroaryl groups include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl, triazolyl and thiadiazolyl groups and benzo-fused analogues thereof. Further examples of heteroaryl groups include tetrazole, 1,2,4-triazine and 1,3,5-triazine. Pyridine rings may be in the N-oxide form.

Where a phenyl group or heteroaryl group bears more than one substituent, preferably not more than one of said substituents is other than halogen or alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

For use in medicine, the compounds of formula I may advantageously be in the form of pharmaceutically acceptable salts. Other

salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, benzenesulphonic acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Alternatively, where the compound of the invention carries an acidic moiety, a pharmaceutically acceptable salt may be formed by neutralisation of said acidic moiety with a suitable base. Examples of pharmaceutically acceptable salts thus formed include alkali metal salts such as sodium or potassium salts; ammonium salts; alkaline earth metal salts such as calcium or magnesium salts; and salts formed with suitable organic bases, such as amine salts (including pyridinium salts) and quaternary ammonium salts.

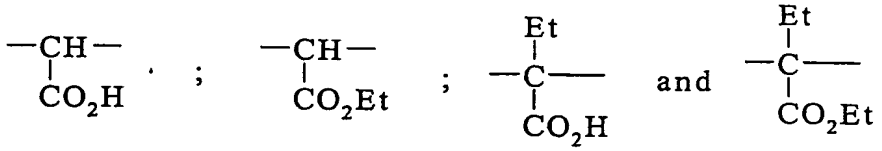
Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In the compounds of formula I, X represents SCN, SR^1, $S(O)R^1$, $(CR^aR^b)_mSO_2R^1$, $SO_2N(R^2)_2$, SO_2NHCOR^1, $SO_2NHN(R^2)_2$, $OSO_2N(R^2)_2$, $OS(O)N(R^2)_2$, OSO_2NHCOR^1, COR^4, $NHCOR^1$, $NHCO_2R^1$, $NHCON(R^2)_2$, $NHSO_2R^1$ or $NHSO_2N(R^2)_2$. In a preferred embodiment, X is selected from SR^1, $(CR^aR^b)_mSO_2R^1$, $SO_2N(R^2)_2$, $OSO_2N(R^2)_2$, COR^4, $NHCOR^1$, $NHCO_2R^1$, $NHCON(R^2)_2$, $NHSO_2R^1$ and $NHSO_2N(R^2)_2$.

When X represents $(CR^aR^b)_mSO_2R^1$, m is 0 or 1. In one embodiment, m is 0. In an alternative embodiment, m is 1.

When m is 1, R^a represents H or C_{1-4}alkyl such as methyl, ethyl or propyl. When m is 1, R^b represents H, C_{1-4}alkyl (such as methyl, ethyl or propyl), CO_2H, C_{1-4}alkoxycarbonyl (such as CO_2Me or CO_2Et) or C_{1-4}alkylsulphonyl (such as methanesulphonyl); or R^b may combine with R^1 to form a 5- or 6-membered ring, in particular a tetrahydrothiophene-1,1-dioxide ring or a tetrahydrothiopyran-1,1-dioxide ring.

When m is 1, preferred identities for the moiety $-CR^aR^b-$ include:



L represents a bond, =CH- or $-(CHR^a)_n-$; but when L represents a bond, X cannot represent $NHCOR^1$, $NHCO_2R^1$ or $NHSO_2R^1$; and when L represents =CH-, X must represent SO_2R^1 or COR^4.

When L represents a bond or $-(CHR^a)_n-$, the moiety -L-X is preferably in the *cis* stereoconfiguration relative to the Ar^1SO_2 moiety.

When L represents $-(CHR^a)_n-$, n is 1, 2 or 3 (preferably 1 or 2), and each R^a is independently H or C_{1-4}alkyl such as methyl or ethyl (especially methyl), but L preferably comprises not more than one R^a group that is other than H.

Particularly preferred examples of L include a bond, $-CH_2-$ and $-CH_2CH_2-$.

R^1 is preferably CF_3, aryl or arylalkyl, or an alkyl, cycloalkyl or cycloalkylalkyl group, optionally substituted as described previously. Preferred substituents include halogen (especially fluorine or chlorine), CF_3, CN, OR^3 (especially OH, OMe and OEt), COR^3 (especially acetyl), CO_2R^3 (especially CO_2H, CO_2Me and CO_2Et) and $CON(R^5)_2$ (especially $CONH_2$).

Examples of alkyl groups represented by R^1 include methyl, ethyl, n-propyl, isopropyl, t-butyl, isobutyl, 2,2,2-trifluoroethyl, cyanomethyl, 2-hydroxyethyl, 2-methoxyethyl, 2-hydroxy-2-methylpropyl, carboxymethyl,

ethoxycarbonylmethyl, 1-carboxyethyl, 1-ethoxycarbonylethyl, carbamoylmethyl and $MeCOCH_2$-.

Examples of cycloalkyl and cycloalkylalkyl groups represented by R^1 include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl and cyclopentylmethyl.

When R^1 represents aryl or arylalkyl, the aryl group may be phenyl or heteroaryl, optionally substituted as defined previously. Preferred substituents include halogen (especially chlorine or fluorine), CF_3, OCF_3, alkyl (especially methyl), OH and alkoxy (especially methoxy). Preferred heteroaryl groups include pyridine, pyrimidine, furan, thiophene, thiazole, imidazole, triazole, thiadiazole and tetrazole.

Examples of aryl groups represented by R^1 include phenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-chlorophenyl, 2-, 3- and 4-hydroxyphenyl, 2-trifluoromethoxyphenyl, 2-methoxyphenyl, 2-pyridyl (and the corresponding N-oxide), 4-pyridyl, 2-pyrimidinyl, 2-furyl, 2-thienyl, 2-thiazolyl, 2-imidazolyl, 2-methylfuran-3-yl, 4-methylthiazol-3-yl, 5-methyl-1,3,4-thiadiazol-2-yl, 1-methylimidazol-2-yl, 1-methyl-1,2,3,4-tetrazol-5-yl, 1,2,4-triazol-3-yl, 1-methyl-1,2,4-triazol-3-yl, 2-methyl-1,2,4-triazol-3-yl and 4-methyl-1,2,4-triazol-3-yl.

Arylalkyl groups represented by R^1 are typically optionally substituted benzyl, phenethyl, heteroarylmethyl or heteroarylethyl groups. Examples include benzyl, 2-furylmethyl, 2-thienylmethyl and 1-(2-thienyl)ethyl.

When X represents SO_2NHCOR^1 or OSO_2NHCOR^1, R^1 is very aptly CF_3, C_{1-6}alkyl or C_{3-6}cycloalkyl, for example methyl.

When X represents $S(O)R^1$, R^1 very aptly represents aryl, for example 2-pyridyl or 1-methyl-1,2,3,4-tetrazol-5-yl.

When X represents $NHCO_2R^1$, R^1 very aptly represents C_{1-6}alkyl (for example methyl) or arylalkyl (for example benzyl).

When X represents $NHCOR^1$, R^1 very aptly represents C_{1-6}alkyl (for example methyl) or substituted C_{1-6}alkyl (for example 2,2,2-trifluoroethyl or 1-hydroxy-2,2,2-trifluoroethyl).

For any $N(R^2)_2$ fragment, preferably either at least one of the R^2 groups represents H or C_{1-6}alkyl such as methyl, or the two R^2 groups complete an N-heterocyclyl group. When one R^2 group represents C_{1-6}alkoxy (such as methoxy), the other preferably represents C_{1-6}alkyl (such as methyl).

When $N(R^2)_2$ does not represent N-heterocyclyl, preferably one R^2 is H or methyl and the other is H, methoxy, aryl (such as phenyl) or optionally substituted alkyl or cycloalkyl. Preferred substituents include CF_3, OR^3 (such as OH and OMe), CO_2R^3 (such as t-butoxycarbonyl) and $OCOR^{3a}$ (such as acetoxy). Within this embodiment, preferred identities for $N(R^2)_2$ include NH_2, $NHMe$, NHEt, NH^iPr, NH^tBu, NMe_2, N(Me)OMe, NHPh, NH-cyclobutyl, $NHCH_2CF_3$, $NHCH_2CO_2{}^tBu$, $NHCH_2CH_2OCOMe$ and $NHCH_2CH_2OH$.

When $N(R^2)_2$ represents N-heterocyclyl, the heterocyclic ring is typically an optionally substituted azetidine, pyrrolidine, 3-pyrroline, piperidine, morpholine, thiomorpholine or 2-aza-5-oxabicyclo[2.2.1]heptane ring. Azetidine and pyrrolidine are preferred, and azetidine is particularly preferred. Preferred substituents include oxo, halogen (especially fluorine), CF_3, OR^3 (especially OH), $OCOR^{3a}$ (especially acetoxy and trimethylacetoxy), OSO_2R^{3a} (especially methanesulphonyloxy), CO_2R^3 (especially CO_2H and CO_2Me), $N(R^5)_2$ (especially dimethylamino) and alkyl (especially methyl). Examples of preferred N-heterocyclyl groups include azetidin-1-yl, pyrrolidin-1-yl, 3-pyrrolin-1-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, 2-aza-5-oxabicyclo[2.2.1]hept-2-yl, 3-oxo-azetidin-1-yl, 3-hydroxyazetidin-1-yl, 3-acetoxyazetidin-1-yl, 3-(dimethylamino)azetidin-1-yl, 3-methanesulphonyloxyazetidin-1-yl, 3,3-difluoroazetidin-1-yl, 3-hydroxy-3-methylazetidin-1-yl, 2-carboxypyrrolidin-1-yl, 2-

methoxycarbonylpyrrolidin-1-yl, 3-fluoropyrrolidin-1-yl, 3,3-difluoropyrrolidin-1-yl, 2-(trifluoromethyl)pyrrolidin-1-yl, 3-oxo-pyrrolidin-1-yl, 3-hydroxypyrrolidin-1-yl, 3-hydroxy-3-methylpyrrolidin-1-yl, 3-(trimethylacetoxy)pyrrolidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl and 4,4-difluoropiperidin-1-yl.

When X represents $SO_2NHN(R^2)_2$, $OS(O)N(R^2)_2$ or $NHCON(R^2)_2$, very aptly both R^2 groups represent methyl, or one R^2 represents H and the other represents C_{1-6}alkyl, such as methyl or ethyl.

In the embodiments in which X represents COR^4, R^4 is selected from $(CR^aR^b)SO_2R^1$, pyridine N-oxide, or phenyl or heteroaryl which is substituted as defined previously.

When R^4 represents $(CR^aR^b)SO_2R^1$, R^a and R^b preferably independently represent H or C_{1-4}alkyl, or R^b together with R^1 completes a 5- or 6-membered ring. Suitable rings include tetrahydrothiophene-1,1-dioxide and tetrahydrothiopyran-1,1-dioxide. Tetrahydrothiophene-1,1-dioxide is preferred. In this context, R^1 is very aptly optionally-substituted C_{1-6}alkyl, especially methyl, or else completes a ring with R^b. Examples of preferred groups represented by R^4 in this embodiment include CH_2SO_2Me, $CH(Me)SO_2Me$, $C(Me)_2SO_2Me$ and 1,1-dioxo-tetrahydrothiophen-2-yl.

When R^4 represents pyridine N-oxide, the pyridine ring may be bonded through the 2-, 3- or 4-position, but the 2-position is preferred.

R^4 may alternatively represent phenyl or heteroaryl, either of which must bear a substituent selected from CO_2H, methylenedioxy, difluoromethylenedioxy, COR^3, C-heterocyclyl, C_{1-4}alkylsulphonyl and substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, OR^3, CO_2R^3, $OCOR^{3a}$, $N(R^5)_2$ and $CON(R^5)_2$. In this context, preferred heteroaryl groups are 5-membered, such as furan, pyrrole and thiophene, furan and pyrrole being particularly preferred and furan most preferred. Examples of preferred substituents include CO_2H, difluoromethylenedioxy, formyl, 1,3-dioxolan-

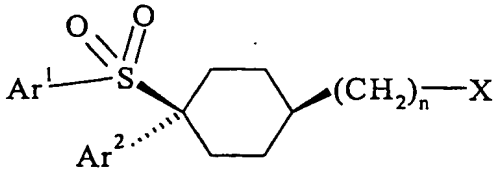
2-yl, methanesulphonyl, hydroxymethyl, allyl, allyloxy, $-(CH_2)_x-CO_2R^3$, $-O(CH_2)_y-CO_2R^3$, $-CH=CH-CO_2R^3$, $-(CH_2)_x-N(R^5)_2$ and $-O(CH_2)_y-N(R^5)_2$, where x is 1, 2 or 3 and y is 2 or 3. In this context R^3 is very aptly H, methyl or ethyl, and $N(R^5)_2$ is very aptly morpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl.

Ar^1 and Ar^2 independently represent optionally substituted phenyl or heteroaryl. Ar^1 is preferably selected from optionally substituted phenyl and optionally substituted 6-membered heteroaryl. Preferred 6-membered heteroaryl embodiments of Ar^1 include optionally substituted pyridyl, in particular optionally substituted 3-pyridyl. Ar^1 is preferably selected from 6-(trifluoromethyl)-3-pyridyl and phenyl which is optionally substituted in the 4-position with halogen, CN, vinyl, allyl, acetyl, methyl or mono-, di- or trifluoromethyl. In one preferred embodiment of the invention Ar^1 represents 4-chlorophenyl. In another preferred embodiment Ar^1 represents 4-trifluoromethylphenyl. In a further preferred embodiment A^1 represents 6-(trifluoromethyl)-3-pyridyl.

Ar^2 preferably represents optionally substituted phenyl, in particular phenyl bearing 2 or 3 substituents selected from halogen, CN, CF_3 and optionally-substituted alkyl. Ar^2 is typically selected from phenyl groups bearing halogen substituents (preferably fluorine) in the 2- and 5-positions or in the 2-, 3- and 6-positions, or from phenyl groups bearing a fluorine substituent in the 2-position and halogen, CN, methyl or hydroxymethyl in the 5-position. In a preferred embodiment of the invention, Ar^2 represents 2,5-difluorophenyl.

In a particular embodiment, Ar^1 is 4-chlorophenyl or 4-trifluoromethylphenyl or 6-(trifluoromethyl)-3-pyridyl and Ar^2 is 2,5-difluorophenyl.

A subclass of the compounds of the invention comprises the compounds of formula II:



II

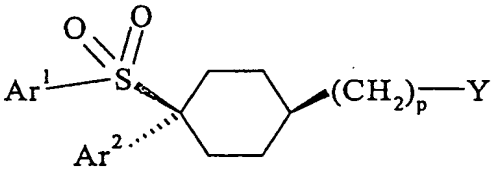
wherein n, X, Ar^1 and Ar^2 have the same definitions and preferred identities as before;

and pharmaceutically acceptable salts thereof.

Preferably n is 1 or 2.

In a subset of the compounds of formula II, X is selected from $NHCOR^1$, $NHCO_2R^1$ and $NHSO_2R^1$ where R^1 has the same definition and preferred identities as before.

A second sub-class of the compounds of the invention comprises the compounds of formula III:



III

wherein p is 0, 1, 2 or 3;

Y is SCN, SR^1, $S(O)R^1$, $(CR^aR^b)_mSO_2R^1$, $SO_2N(R^2)_2$, SO_2NHCOR^1, $SO_2NHN(R^2)_2$, $OSO_2N(R^2)_2$, $OS(O)N(R^2)_2$, OSO_2NHCOR^1, COR^4, $NHCON(R^2)_2$ or $NHSO_2N(R^2)_2$;

and m, R^a, R^b, R^1, R^2, R^4, Ar^1 and Ar^2 have the same definitions and preferred identities as before;

and pharmaceutically acceptable salts thereof.

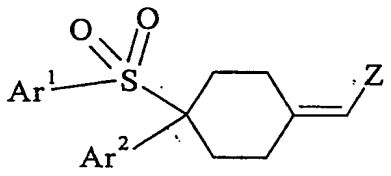
Preferably p is 0, 1 or 2.

In a subset of the compounds of formula III, Y is selected from SCN, SR^1, $S(O)R^1$, $(CR^aR^b)_mSO_2R^1$, $SO_2N(R^2)_2$, SO_2NHCOR^1 and $SO_2NHN(R^2)_2$; preferably from SCN, SR^1, $(CR^aR^b)_mSO_2R^1$ and $SO_2N(R^2)_2$; and most preferably from $(CR^aR^b)_mSO_2R^1$ and $SO_2N(R^2)_2$. Within this subset, p is preferably 1 or 2. In one preferred embodiment Y is $(CR^aR^b)_mSO_2R^1$. In

another preferred embodiment Y is $SO_2N(R^2)_2$, in which case p is very aptly 1 and $N(R^2)_2$ is very aptly N-heterocyclyl.

In a second subset of the compounds of formula III, Y is selected from $OSO_2N(R^2)_2$, $OS(O)N(R^2)_2$, OSO_2NHCOR^1, $NHCON(R^2)_2$, $NHSO_2N(R^2)_2$ and COR^4. Within this subset, p is preferably 0 or 1. In one preferred embodiment p is 0 and Y is $OSO_2N(R^2)_2$. In another preferred embodiment, p is 1 and Y is $NHCON(R^2)_2$. In a further preferred embodiment, p is 1 and Y is COR^4. In a further preferred embodiment, p is 0 and Y is $NHSO_2N(R^2)_2$. In a further preferred embodiment, p is 1 and Y is $NHSO_2N(R^2)_2$.

A third sub-class of the compounds of the invention comprises the compounds of formula IV:



IV

wherein Z represents SO_2R^1 or COR^4;

and R^1, R^4, Ar^1 and Ar^2 have the same definitions and preferred identities as before;

and pharmaceutically acceptable salts thereof.

In a preferred embodiment, Z is SO_2R^1.

Examples of individual compounds in accordance with the invention are provided in the Examples section appended hereto.

The compounds of formula I have an activity as modulators of the processing of APP by γ-secretase.

The invention also provides pharmaceutical compositions comprising one or more compounds of formula I or the pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or

suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums or surfactants such as sorbitan monooleate, polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 250 mg, for example 1, 2, 5, 10, 25, 50, 100, 200 or 250 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil or coconut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(vinylpyrrolidone) or gelatin.

The present invention also provides a compound of formula I or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human body. Preferably the treatment is for a condition associated with the deposition of β-amyloid. Preferably the condition is a neurological disease having associated β-amyloid deposition such as Alzheimer's disease.

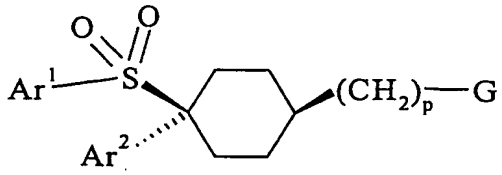
The present invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing Alzheimer's disease.

The present invention further provides a method of treatment of a subject suffering from or prone to a condition associated with the deposition of β-amyloid which comprises administering to that subject an effective amount of a compound according to formula I or a pharmaceutically acceptable salt thereof. Preferably the condition is a neurological disease having associated β-amyloid deposition such as Alzheimer's disease.

For treating or preventing Alzheimer's Disease, a suitable dosage level is about 0.01 to 250 mg/Kg per day, preferably about 0.10 to 100 mg/Kg per day, especially about 1.0 to 50 mg/Kg, and for example about 10 to 30 mg/Kg of body weight per day. Thus, a dose of about 500mg per person per day may be considered. The compounds may be administered

on a regimen of 1 to 4 times per day. In some cases, however, dosage outside these limits may be used.

Compounds of formula I in which L is $-(CH_2)_p-$ and X represents SCN, SR^1 or $(CR^aR^b)_mSO_2R^1$ may be prepared by reaction of, respectively, MSCN, MSR^1 or $M(CR^aR^b)_mSO_2R^1$ with a compound of formula (1):

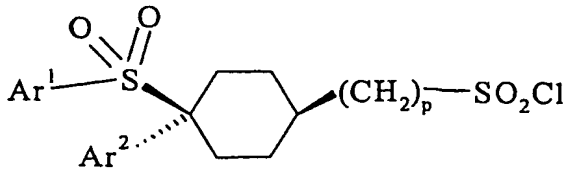


(1)

where M is a metal cation (preferably an alkali metal cation, such as Li or Na), G is a leaving group, and R^1, R^a, R^b, Ar^1, Ar^2, m and p have the same meanings as before. Suitable identities for G include halide (especially bromide or iodide) and alkyl- or arylsulphonate. Iodide and mesylate are particularly suitable. The metallated derivatives MSR^1 and $M(CR^aR^b)_mSO_2R^1$ may be generated by reaction of the corresponding hydrides with NaOH, LiOH, NaH, BuLi, $LiN(^iPr)_2$ or similar, and are typically reacted *in situ* with the compounds (1).

Compounds of formula I in which X represents $S(O)R^1$ may be prepared from the corresponding compounds in which X represents SR^1 by oxidation with one equivalent of m-chloroperoxybenzoic acid. The oxidation takes place at ambient temperature in a dichloromethane-water mixture. Oxidation of the same compounds with two equivalents of m-chloroperoxybenzoic acid, or with sodium periodate in the presence of RuO_2 catalyst, provides an alternative route to compounds in which X represents $(CR^aR^b)_mSO_2R^1$ and m is 0.

Compounds of formula I in which L is $-(CH_2)_p-$ and X represents , $SO_2N(R^2)_2$ or $SO_2NHN(R^2)_2$ may be prepared by reaction of $(R^2)_2NH$ or $(R^2)_2NNH_2$ respectively with a sulphonyl chloride of formula (2):

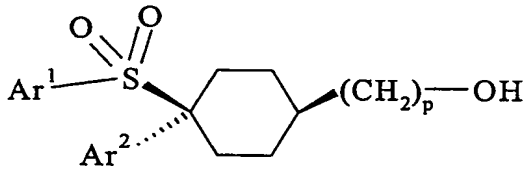


(2)

where R^2, Ar^1, Ar^2 and p have the same meanings as before. The reaction is typically carried out in dichloromethane at ambient temperature, either using excess of the amine or using an additional base such as potassium carbonate, pyridine or triethylamine.

Compounds of formula I in which X represents SO_2NHCOR^1 may be prepared from the corresponding compounds in which X represents SO_2NH_2 by coupling with R^1CO_2H. Any of the standard peptide coupling procedures may be used, for example the use of dimethylaminopyridine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

Compounds of formula I in which L is $-(CH_2)_p-$ and X represents $OSO_2N(R^2)_2$ may be prepared by reaction of a sulphamoyl chloride $(R^2)_2NSO_2Cl$ with an alcohol of formula (3):



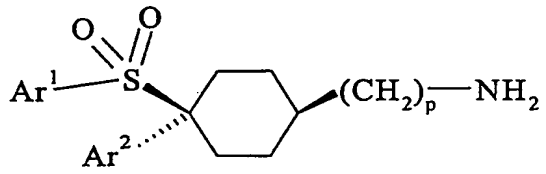
(3)

where R^2, Ar^1, Ar^2 and p have the same meanings as before. The reaction is typically carried out in dichloromethane at ambient temperature in the presence of a base such as pyridine or triethylamine. The sulphamoyl chlorides $(R^2)_2NSO_2Cl$ are available by reaction of $(R^2)_2NH$ with sulphuryl chloride in acetonitrile at ambient temperature.

Compounds of formula I in which X represents OSO_2NHCOR^1 may be prepared from the corresponding compounds in which X represents OSO_2NH_2 by coupling with R^1CO_2H. Any of the standard peptide coupling procedures may be used, for example the use of dimethylaminopyridine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

Compounds of formula I in which L is $-(CH_2)_p-$ and X represents $OS(O)N(R^2)_2$ may be prepared by treating an alcohol of formula (3) first with thionyl chloride, and then with $(R^2)_2NH$. The reaction with thionyl chloride is typically carried out at –78°C, and the resulting intermediate reacted in situ with the amine at the same temperature, then allowed to warm to ambient temperature.

Compounds of formula I in which L is $-(CH_2)_p-$ and X represents $NHCOR^1$, $NHCO_2R^1$, $NHSO_2R^1$ or $NHSO_2N(R^2)_2$ may be prepared by reacting an amine of formula (4) with, respectively, R^1COCl, R^1OCOCl, R^1SO_2Cl and $(R^2)_2NSO_2Cl$:

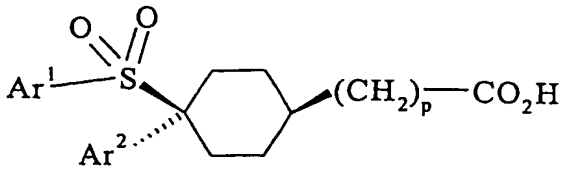


(4)

where R^1, Ar^1, Ar^2 and p have the same meanings as before. The reaction is typically carried out in dichloromethane at ambient or reduced temperature, in the presence of a base such as pyridine or triethylamine. Alternatively, the compounds in which X represents $NHCOR^1$ may be prepared by coupling of amines (4) with R^1CO_2H. Any of the standard peptide coupling procedures may be used, for example the use of 1-hydroxybenzotriazole or dimethylaminopyridine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

An alternative route to the compounds of formula I in which L is $-(CH_2)_p-$ and X represents $NHSO_2N(R^2)_2$ involves reacting an amine of formula (4) with catechol sulphate and reacting the resulting sulphamate with $(R^2)_2NH$. The first step is typically carried out in THF at 0°C, and the second step at 80°C in dioxan.

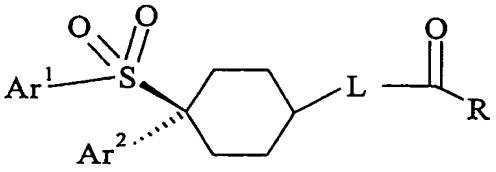
Compounds of formula I in which L is $-(CH_2)_p-$ and X represents $NHCON(R^2)_2$ may be prepared by treating an carboxylic acid of formula (5) first with diphenylphosphoryl azide, and then with $(R^2)_2NH$:



(5)

where R^2, Ar^1, Ar^2 and p have the same meanings as before. The first step is typically carried out in toluene at 110°C in the presence of triethylamine, and the second step at ambient temperature in the same solvent.

Compounds of formula I in which X represents COR^4, and R^4 represents substituted phenyl or heteroaryl, may be prepared by reaction of a compound of formula (6a) with R^4-M^1:



(a) R = N(Me)-OMe

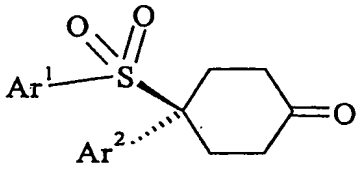
(b) R = OEt

(6)

where M^1 represents Li or MgBr and Ar^1, Ar^2 and L have the same meanings as before. The reaction is typically carried out in THF or diethyl ether at reduced temperature. When M^1 is MgBr, R^4 preferably represents substituted phenyl.

Compounds of formula I in which X represents COR^4, and R^4 represents $(CR^aR^b)SO_2R^1$, may be prepared by reaction of a compound of formula (6b) with R^4-Li. The reaction is typically carried out in THF or diethyl ether at reduced temperature.

Compounds of formula I in which L represents =CH- and X represents SO_2R^1 may be prepared by reaction of a cyclohexanone (7):



(7)

with CH_3-SO_2R^1, followed by dehydration of the resulting tertiary alcohol; where R^1, Ar^1 and Ar^2 have the same meanings as before. The first step is typically carried out in THF at –78°C in the presence of strong base such as lithium diisopropylamide. The dehydration may be effected by converting the alcohol to the corresponding mesylate and treating the latter with 1,8-diazabicyclo[5.4.0]undec-7-ene in THF at ambient temperature.

The compounds of formula (1) in which G is iodide may be obtained by reaction of the corresponding compounds of formula (5) with iodosobenzene diacetate and iodine under irradiation. The compounds of formula (1) in which G is alkyl- or arylsulphonate are available from the reaction of the corresponding compounds of formula (3) with the appropriate sulphonyl chloride.

The sulphonyl chlorides of formula (2) may be obtained by reaction of the compounds of formula (1) with potassium thioacetate, hydrolysis of the resulting thioester to give the corresponding thiol, then treatment of the thiol with potassium nitrate and sulphuryl chloride.

The alcohols of formula (3) in which p is 1, 2 or 3 are available by reduction of the acids of formula (5), the value of p increasing by 1 in the process. The alcohols of formula (3) in which p is 0 are available from the reduction of the cyclohexanones of formula (7). Reduction with L-Selectride™ provides the *cis* isomer selectively. Reduction with sodium borohydride provides a mixture of *cis* and *trans* isomers which may be separated by chromatography.

The amines of formula (4) are available from the carboxylic acids (5) by sequential reaction with oxalyl chloride, sodium azide and benzyl alcohol, followed by hydrolysis of the resulting carbamate. Alternatively, they may be obtained from the mesylates of the alcohols (3) by displacement with azide ion, followed by reduction.

The carboxylic acids of formula (5) in which p is 0 are available from the alcohols (3) in which p is 0 by formation of the mesylate ester, followed

by nucleophilic displacement with cyanide ion and hydrolysis of the resulting nitrile. The corresponding acids in which p is 1 are formed by condensation of cyclohexanones (7) with ethyl (diethoxyphosphinyl)acetate, followed by reduction of the resulting alkenyl ester (i.e. (6b) where L is =CH-) and hydrolysis of the ester group. The corresponding acids in which p is 2 or 3 are obtainable by standard methods of homologation. For example, reduction of an acid (5) in which p is 1 provides an alcohol (3) in which p is 2, and mesylation, displacement with cyanide, and hydrolysis provides the corresponding acid in which p is 2. Repeating this process provides the acid (5) in which p is 3.

The N-methoxyamides (6a) are obtained from the corresponding carboxylic acids by treatment first with oxalyl chloride and then with N,O-dimethylhydroxylamine.

Detailed procedures for the synthesis of compounds of formulae (1) (6), and cyclohexanones (7), are provided in WO 02/081435 and US 2003/0114496 A1.

It will be apparent to those skilled in the art that individual compounds of formula I prepared by the above routes may be converted into other compounds in accordance with formula I by means of well known synthetic techniques such as alkylation, esterification, amide coupling, hydrolysis, oxidation and reduction. Such techniques may likewise be carried out on precursors of the compounds of formula I. For example, a compound of formula I in which X is SCN may be treated with trimethyl(trifluoromethyl)silane and tetrabutylammonium fluoride to provide the corresponding compound in which X is SCF_3, which in turn may be oxidised to the corresponding compound wherein X is SO_2CF_3. Similarly, a compound of formula I wherein X is $(CR^aR^b)SO_2R^1$ or $CO(CR^aR^b)SO_2R^1$ and one or both of R^a and R^b is H may be alkylated so as to provide the corresponding compound in which one or both of R^a and R^b is alkyl. Alternatively, if in the aforesaid compound R^b is CO_2H,

decarboxylation via refluxing with sodium chloride in DMSO provides the corresponding compound in which R^b is H.

Also, substituents on the aromatic groups Ar^1 or Ar^2 may be added or interconverted by means of standard synthetic processes carried out on the compounds of formula I or their precursors. For example, in esters (6b) a chlorine or bromine atom on Ar^1 or Ar^2 may be replaced by vinyl by treatment with vinyltributyltin in the presence of tri-t-butylphosphine, cesium fluoride and tris(dibenzylideneacetone)dipalladium(0). Ozonolysis of the vinyl group provides the corresponding formyl derivative, which may be transformed in a variety of ways, including oxidation to the corresponding acid, reduction to the corresponding benzyl alcohol, and conversion to the corresponding nitrile by treatment with hydroxylamine then triphenylphosphine and carbon tetrachloride.

Compounds of formula I in which L comprises a pendant alkyl group are obtainable by alkylation of the corresponding compounds wherein L is $-(CH_2)_n-$, or by alkylation of a precursor such as an ester (6b) wherein L is $-(CH_2)_n-$.

Pyridine groups may be oxidised to the corresponding N-oxides by treatment with urea hydrogen peroxide and trifluoroacetic anhydride in dichloromethane at 0°C.

Where they are not themselves commercially available, the starting materials and reagents employed in the above-described synthetic schemes may be obtained by the application of standard techniques of organic synthesis to commercially available materials.

It will be appreciated that many of the above-described synthetic schemes may give rise to mixtures of stereoisomers. Such mixtures may be separated by conventional means such as fractional crystallisation and preparative chromatography.

Certain compounds according to the invention may exist as optical isomers due to the presence of one or more chiral centres or because of the overall asymmetry of the molecule. Such compounds may be prepared in

racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallisation and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 3rd ed., 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

An assay which can be used to determine the level of activity of compounds of the present invention is described in WO01/70677. A preferred assay to determine such activity is as follows:

1) SH-SY5Y cells stably overexpressing the βAPP C-terminal fragment SPA4CT, are cultured at 50-70% confluency. 10mM sodium butyrate is added 4 hours prior to plating.

2) Cells are plated in 96-well plates at 35,000 cells/well/100μL in Dulbecco's minimal essential medium (DMEM) (phenol red-free) + 10% foetal bovine serum (FBS), 50mM HEPES buffer (pH7.3), 1% glutamine.

3) Make dilutions of the compound plate. Dilute stock solution 18.2x to 5.5% DMSO and 11x final compound concentration. Mix compounds vigorously and store at 4°C until use.

4) Add 10μL compound/well, gently mix and leave for 18h at 37°C, 5% CO_2.

5) Prepare reagents necessary to determine amyloid peptide levels, for example by Homogeneous Time Resolved Fluorescence (HTRF) assay.

6) Plate 160μL aliquots of HTRF reagent mixture to each well of a black 96-well HTRF plate.

7) Transfer 40μL conditioned supernatant from cell plate to HTRF plate. Mix and store at 4°C for 18 hours.

8) To determine if compounds are cytotoxic following compound administration, cell viability is assessed by the use of redox dye reduction. A typical example is a combination of redox dye MTS (Promega) and the electron coupling reagent PES. This mixture is made up according to the manufacturer's instructions and left at room temperature.

9) Add 10μL/well MTS/PES solution to the cells; mix and leave at 37°C.

10) Read plate when the absorbance values are approximately 0.4 – 0.8. (Mix briefly before reading to disperse the reduced formazan product).

11) Quantitate amyloid beta 40 peptide using an HTRF plate reader.

Alternative assays are described in *Biochemistry*, 2000, 39(30), 8698-8704.

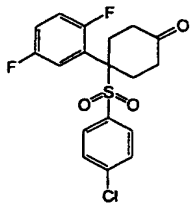
See also, *J. Neuroscience Methods*, 2000, 102, 61-68.

The Examples of the present invention all had an ED_{50} of less than 1μM, typically less than 0.5μM, in most cases less than 100nM, and in preferred cases less than 10nM, in at least one of the above assays.

The following examples illustrate the present invention.

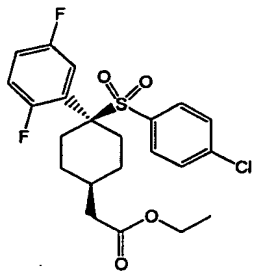
Examples

Intermediate A: 4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl) cyclohexanone



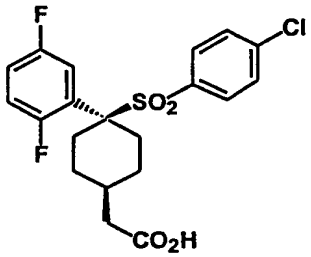
Prepared as described in WO 02/081435 (Example 2).

Intermediate B: [4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-acetic acid ethyl ester



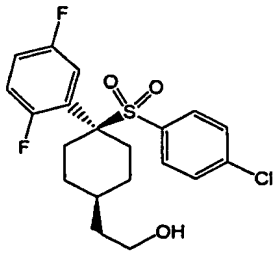
Prepared as described in WO 02/081435 (Example 48).

Intermediate C: [4-(4-Chlorophenylsulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-acetic acid



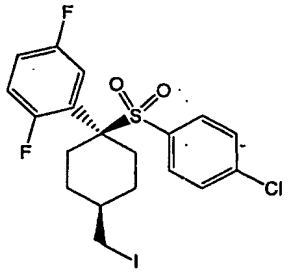
Prepared as described in WO 02/081435 (Example 50).

Intermediate D: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-ethanol



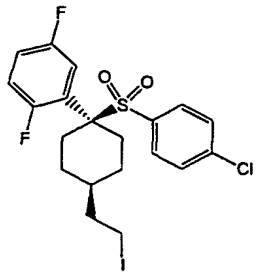
To Intermediate C (1 g, 2.3 mmol) in dry tetrahydrofuran (80 mL) at 0°C under nitrogen were added triethylamine (0.4 mL, 2.8 mmol) and *iso*-butylchloroformate (0.36 mL, 2.8 mmol). The reaction was stirred for 1.5 h, filtered, the filtrate re-cooled to 0°C and sodium borohydride (435 mg, 11 mmol) in water (10 mL) added dropwise. After stirring at 0°C for 1 h the reaction was concentrated, diluted with ethyl acetate, washed with water and brine and then dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography on silica, eluting with *iso*-hexane/ethyl acetate (1:1), to give the alcohol as a white solid (960 mg

Intermediate E: Iodo-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-methane



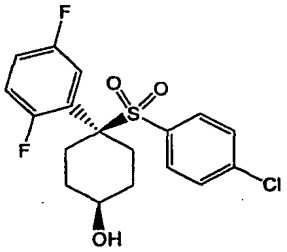
A stirred solution of Intermediate C (6.85 g, 16.0 mmol.), iodosobenzene diacetate (14.4 g, 44.7 mmol.) and iodine (6.20 g, 24 mmol.) in dry benzene (200 mL) was heated to reflux under irradiation by a 250W tungsten lamp. After 45 minutes, further iodosobenzene diacetate (3.0 g, 9.3 mmol.) and iodine (1.5 g, 5.8 mmol.) were added and reflux under irradiation continued for a further 1h. The reaction was cooled and diluted with ethyl acetate (200 mL) then washed with aqueous sodium thiosulfate (10%, 2 x 200 mL), water (200 mL), aqueous sodium hydroxide solution (1M, 200 mL) and brine (200 mL) then dried ($MgSO_4$) and evaporated to leave a residue which was purified by flash column chromatography on silica, eluting with ether:dichloromethane:iso-hexane (1:1:8), to afford iodo-[4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-methane (6.00 g, 74%).

Intermediate F: 2-Iodo-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-ethane



A solution of Intermediate D (414 mg, 1 mmol), imidazole (272 mg, 4 mmol) and triphenylphosphine (524 mg, 2 mmol) in toluene (15 mL) was stirred at room temperature for 10 minutes, then iodine (279 mg, 1.1 mmol) was added. The reaction was stirred at ambient temperature for 2.5h then at 65°C for 1h. Upon cooling, the mixture was decanted and evaporated to dryness. The residue was extracted into ether (3 x 50 mL) and the combined organics evaporated then filtered through a plug of silica, eluting with ether:iso-hexane (1:4) to give the desired iodide (252 mg).

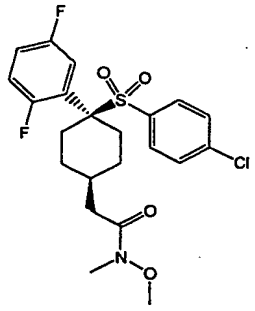
Intermediate G: 4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexanol



A solution of Intermediate A (10.05 g, 26 mmol) in tetrahydrofuran (200 mL) cooled to –78°C was treated with L-Selectride™ (1.0 M solution in tetrahydrofuran, 31.4 mL, 31.4 mmol). After stirring at –78°C for 2 hours the reaction was quenched with aqueous hydrochloric acid (2M). The solvent was evaporated and the product extracted into ethyl acetate and washed with water followed by brine, and evaporated to an oil which

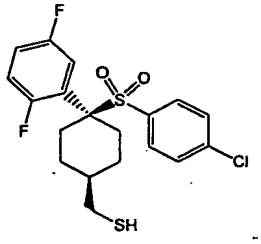
was purified by flash chromatography eluting with ethyl acetate:hexane 1:1 to afford the desired intermediate (6g).

Intermediate H: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-N-methoxy-N-methyl-acetamide



Prepared as described in WO 02/081435 (Example 219).

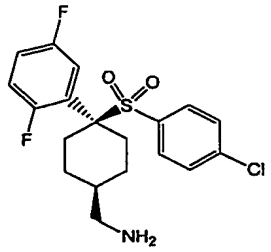
Intermediate I: [4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-methanethiol



To a solution of Intermediate E (2.05 g, 4.0 mmol.) in *N,N*-dimethylformamide (80 mL) was added potassium thioacetate (2.3 g, 20 mmol.) and the solution stirred for 2h. at ambient temperature then diluted with water (100 mL) and extracted into ether (2 x 100 mL). The combined organic layers were washed with water (3 x 100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated to leave the crude thioacetic acid 4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexylmethyl ester (1.81 g). This was dissolved in methanol (80 mL), 1M aqueous sodium hydroxide solution (20 mL) was added and the mixture vigorously stirred for 1h. Water (50 mL) was added and the mixture extracted into ethyl acetate (2 x 100 mL). The combined organic layers were washed with

water (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated to leave a residue of the desired thiol (1.65g, quant.).

Intermediate J: C-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-methylamine

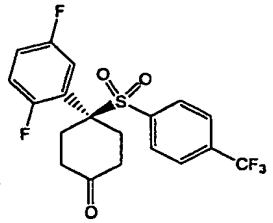


To a stirred solution of Intermediate C (75 mg, 0.18 mmol.) in tetrahydrofuran (10 mL) was added oxalyl chloride (0.02 mL, 0.23 mmol.) and *N,N*-dimethylformamide (1 drop) and the mixture stirred at ambient temperature for 90 minutes then evaporated. Toluene (10 mL) was added then evaporated and the residue taken up in benzene (2 mL) and cooled in an ice bath. A solution of tetrabutylammonium bromide (1 mg) and sodium azide (23 mg, 0.36 mmol.) in water (1 mL) was added, the cooling bath removed and the mixture allowed to stir at ambient temperature for 2 hours. The layers were separated and the organic phase washed with brine (10 mL), dried ($MgSO_4$) and filtered. Benzyl alcohol (0.1 mL) was added and the mixture heated to reflux for 18 hours then cooled and diluted with ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated to leave a residue which was purified by flash column chromatography on silica, eluting with ethyl acetate:iso-hexane (1:3), to afford the desired benzyl carbamate (60mg). MS (ES+) 534 ($[MH]^+$).

To the foregoing carbamate (40 mg, 0.08 mmol.) was added hydrobromic acid (1 mL of a 45% w/v solution in acetic acid). The reaction was stirred for 90 minutes, diethyl ether (10 mL) and water (10 mL) added, the organic phase washed with aqueous hydrochloric acid (2N, 10 mL), the combined aqueous phases basified to pH 12 with 4N aqueous

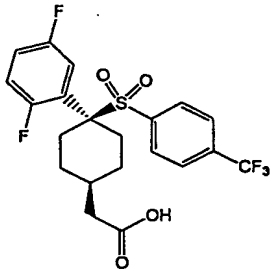
sodium hydroxide solution then extracted into ethyl acetate (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give the primary amine intermediate (26 mg) which was used without further purification.

Intermediate K: 4-(2,5-Difluoro-phenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexanone



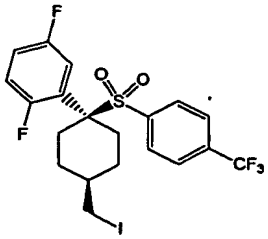
Prepared as described in WO 02/081435 (Example 41).

Intermediate L: [4-(2,5-Difluoro-phenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-acetic acid



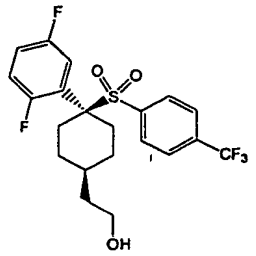
Prepared as described in WO 02/081435 (Example 232).

Intermediate M: Iodo-[4-(2,5-Difluoro-phenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-methane



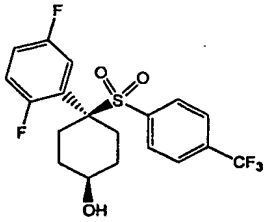
Prepared from Intermediate L by the method of Intermediate E

Intermediate N: 2-[4-(2,5-Difluoro-phenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-ethanol



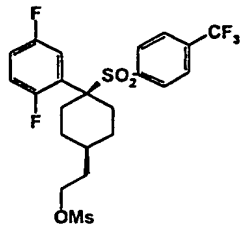
Intermediate L (14.1 g, 0.031 mol) in tetrahydrofuran (250 mL) was treated with triethylamine (5.1 mL, 0.036 mol) and ⁱbutylchloroformate (4.64 mL, 0.036 mol) at 0°C. After stirring for 1.5 hours, the precipitate was filtered off and the filtrate re-cooled to 0°C, before being treated with sodium borohydride (1.9g, 0.05 mol) in water (10 mL) and stirred for 1 hour. The reaction was concentrated, diluted with ethyl acetate and washed with water and brine. The separated organic phase was dried over magnesium sulfate, filtered and evaporated to dryness. The alcohol was purified by silica gel chromatography eluting with ethyl acetate and hexane mixtures to give 11.5g.

Intermediate O: 4-(2,5-Difluoro-phenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexanol



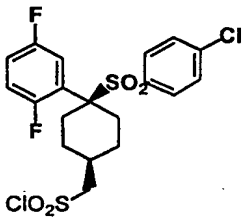
Prepared from Intermediate K by the method of Intermediate G.

Intermediate P: Methanesulfonic acid 2-[4-(2,5-difluoro-phenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-ethyl ester



Intermediate N (3.80 g, 8.48 mmol) and triethylamine (1.17 mL) in dichloromethane (150 mL) was treated dropwise with mesyl chloride, maintaining the internal temperature below –40°C. After complete addition the reaction was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was washed with water (50 mL), 10% aqueous citric acid (50 mL) and saturated sodium bicarbonate solution (50 mL) then dried over magnesium sulfate. After evaporation to dryness, the product was triturated with diethyl ether to give 4.2g.

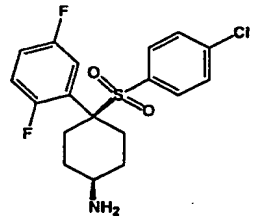
Intermediate Q: [4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-methanesulfonyl chloride



Intermediate I (1.65 g, 4.0 mmol.) in acetonitrile (120 mL) was cooled to 0°C under nitrogen. Potassium nitrate (1.01 g, 10 mmol.) then sulfuryl chloride (0.80 mL, 10 mmol.) were added, the mixture stirred at 0°C for 2 hours, then diluted with a saturated aqueous solution of sodium hydrogencarbonate (100 mL). The mixture was extracted into ethyl acetate (2 x 100 mL) and the combined organics washed with saturated aqueous sodium hydrogencarbonate (100 mL) and brine (100 mL), dried

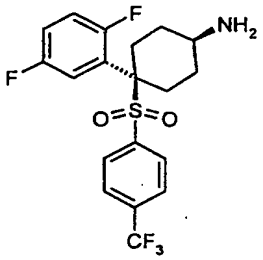
($MgSO_4$) and evaporated to leave a residue which was purified by column chromatography on silica, eluting with diethyl ether : iso-hexane (1:2), to afford the title compound as a colourless solid (0.81g).

Intermediate R: 4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexylamine



Prepared as described in WO 02/081435 (Example 39).

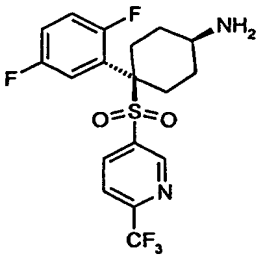
Intermediate S: 4-(2,5-Difluorophenyl)-4-(4-trifluoromethylbenzenesulfonyl)-cyclohexylamine



Prepared as for Intermediate R, using Intermediate K, except that the borohydride reduction was carried out at –20°C.

MS (ES+) MH+ 420

Intermediate T: 4-(2,5-Difluorophenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexylamine



(1) A solution of 3-amino-6-(trifluoromethyl)pyridine (1.62 g, 0.01 mol) in concentrated hydrochloric acid (1.7 mL), was treated with ice (2 g) and cooled to 0°C. Sodium nitrite (0.71 g, 0.01 mol) in water (2 mL) was added slowly, the reaction mixture stirred for 5 minutes at 0°C then treated slowly with a solution of potassium ethyl xanthate (1.92 g, 0.012 mol) in ethanol-water. The reaction mixture was heated at 50-55°C for 30 minutes, cooled and diluted with diethyl ether and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The resulting xanthate was dissolved in ethanol (30 mL) and treated with potassium hydroxide (3 g) and refluxed (90°C) for 2 h. After cooling and filtering, the filtrate was acidified with citric acid and diluted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography on silica gave the (trifluoromethyl)pyridinethiol as a yellow oil (0.79 g, 44%).

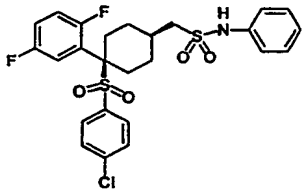
(2) This thiol (0.5 g, 2.8 mmol) was reacted first with 2,5-difluorobenzyl bromide and subsequently with 3-chloroperoxybenzoic acid by the procedure described for Intermediate 1 in WO 02/081435 to gave the pyridyl benzyl sulfone as a white powder (0.82 g, 87% over 2 steps).

(3) This sulfone (50 mg, 0.15 mmol) in tetrahydrofuran (5 mL) at 0°C was treated with potassium *tert*-butoxide (17 mg, 0.15 mmol), then with 2,2-bis(2-iodoethyl)-1,3-dioxolane (H. Niwa et al, J. Am. Chem. Soc., 1990, 112, 9001) (86 mg, 0.23 mmol), stirred for 1 h at room temperature and then for 1 h at 70°C. The cooled reaction mixture was treated with more potassium *tert*-butoxide (1.2 equivalents) and 2,2-bis(2-iodoethyl)-1,3-dioxolane (0.3 equivalents). After heating at 70°C for 1h, then cooling to room temperature, the reaction mixture was diluted with diethyl ether and water, the layers separated and the organic layer washed with water and brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography on silica gave the desired cyclohexanone cyclic ketal (38 mg, 56%) as a white solid.

(4) This ketal (30 mg, 0.065 mmol) was heated at 50°C overnight with *p*-toluenesulfonic acid (15 mg) in 80% acetic acid-water. The reaction mixture was partitioned between diethyl ether and water and the organic layer washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography on silica gave the cyclohexanone (25 mg, 92%) as a white solid.

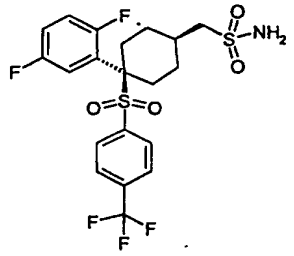
(5) The cyclohexanone was converted to the title amine by the procedure of Intermediate R, except that the borohydride reduction was carried out at –78°C. M/Z 421 (MH^+).

Example 1: C-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-N-phenyl-methanesulfonamide



Prepared from Intermediate Q and excess aniline by refluxing in tetrahydrofuran under nitrogen. MS (ES+) 562 ($[MNa]^+$).

Example 2: [4-(2,5-Difluoro-phenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-methanesulfonamide



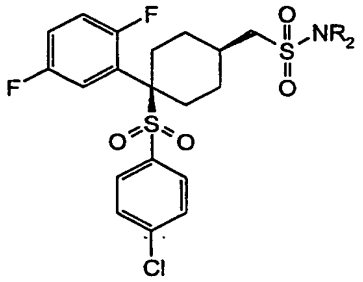
Intermediate M (650 mg, 1.3 mmol) was converted to the corresponding thiol and then to the corresponding sulfonyl chloride by the methods of Intermediate I and Intermediate Q. (Yield 365 mg white solid). This was dissolved in dichloromethane (30 mL) and ammonia gas bubbled into the

solution until saturation. The reaction was stirred for a further 30 min before filtering through Celite®. After concentration, the residue was purified by flash chromatography on silica, eluting with *iso*-hexane/ethyl acetate (1:1), to give the sulfonamide as a white solid (150 mg).

MS (ES+) 498 ([MH]+).

Examples 3- 33

The sulfonamides in examples 3-33 were prepared from Intermediate Q by treatment with the appropriate amine in dichloromethane. The reaction was diluted with ethyl acetate, washed with 2N HCl and brine, dried ($MgSO_4$) and evaporated to leave a residue which was purified by column chromatography on silica. In cases where a salt of the required amine is used, a base, for example pyridine or potassium carbonate, may be added.



Example	-NR_2	MS (ES+)
3	amino	486 ([MNa]+)
4	cyclobutylamino	540 ([MNa]+)
5	piperidin-1-yl	532 ([MH]+)
6	2-trifluoromethylpyrrolidin-1-yl	603 ([MNH_4]+)
7	3,3-difluoropyrrolidin-1-yl	554 ([MH]+)
8	(R)-3-fluoropyrrolidin-1-yl	536 ([MH]+)
9	(S)-3-fluoropyrrolidin-1-yl	536 ([MH]+)
10	5-aza-2-oxabicyclo[2.2.1]hept-5-yl	546 ([MH]+)
11	4,4-difluoropiperidin-1-yl	585 ([MNH_4]+)
12	N-methoxy-N-methylamino	530 ([MNa]+)
13	morpholin-4-yl	534 ([MH]+)

Example	-NR_2	MS (ES^+)
14	pyrrolidin-1-yl	518 ($[MH]^+$)
15	azetidin-1-yl	504 ($[MH]^+$)
16	t-butylamino	537 ($[MNH_4]^+$)
17	2,2,2-trifluoroethylamino	568 ($[MNa]^+$)
18	(R)-2-(methoxycarbonyl)pyrrolidin-1-yl	576 ($[MH]^+$)
19	(S)-2-(methoxycarbonyl)pyrrolidin-1-yl	576 ($[MH]^+$)
20	t-butoxycarbonylmethylamino	600 ($[MNa]^+$)
21	hydrazinyl	479 ($[MH]^+$)
22	dimethylamino	492 ($[MH]^+$)
23	isopropylamino	528 ($[MNa]^+$)
24	3,3-difluoroazetidin-1-yl	540 ($[MH]^+$)
25[a]	(R)-2-carboxypyrrolidin-1-yl	562 ($[MH]^+$)
26[a]	(S)-2-carboxypyrrolidin-1-yl	562 ($[MH]^+$)
27[b]	glycinyl	522 ($[MH]^+$)
28[c]	acetylamino	528 ($[MNa]^+$)
29	3-acetoxyazetidin-1-yl	562 ($[MH]^+$)
30[a]	3-hydroxyazetidin-1-yl	520 ($[MH]^+$)
31[d]	3-oxo-azetidin-1-yl	535 ($[MNH_4]^+$)
32[e]	3-hydroxy-3-methyl-azetidin-1-yl	534 ($[MH]^+$)
33[f]	3-methanesulfonyloxy-azetidin-1-yl	598 ($[MH]^+$)

(a) – hydrolysis of Ex. 18, 19 or 29 using LiOH in aqueous THF.

(b) - treatment of Ex. 20 with trifluoroacetic acid in dichloromethane.

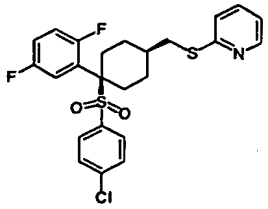
(c) – coupling of Ex. 27 with acetic acid using dimethylaminopyridine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in dichloromethane.

(d) – oxidation of Ex.30 using Dess-Martin periodinane in dichloromethane at ambient temperature.

(e) – treatment of Ex. 31 with MeMgBr in THF at ambient temperature.

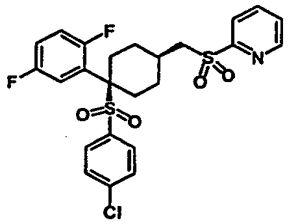
(f) – treatment of Ex. 30 with methanesulfonyl chloride and triethylamine in dichloromethane at 0°C.

Example 34: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexylmethylsulfanyl]-pyridine



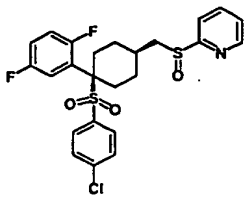
To a stirred solution of Intermediate E (150 mg, 0.29 mmol) in ethanol (10 mL) under nitrogen was added potassium hydroxide (18 mg, 0.32 mmol) and 2-mercaptopyridine (36 mg, 0.32 mmol). The mixture was stirred and heated to reflux for 16 hours. After cooling, the reaction was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and evaporated to leave a residue (154 mg) which was purified by preparative thin layer chromatography eluting with ethyl acetate: iso-hexane 1:6 to afford the desired product (118 mg). MS (ES+) 494 ($[MH]^+$), 318 ($[M-ArSO_2-]^+$).

Example 35: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexylmethanesulfonyl]-pyridine



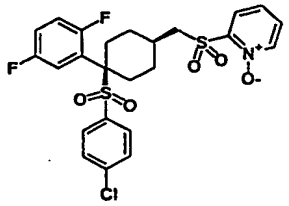
To a stirred solution of the product from Example 34 (40 mg, 0.081 mmol) in dichloromethane (10 mL) under nitrogen was added 3-chloroperoxybenzoic acid (62 mg, 50-55% w/w in water, 0.18 mmol). The mixture was stirred at ambient temperature for 18h. The reaction was diluted with dichloromethane, washed with sodium sulfite solution and brine, dried ($MgSO_4$) and evaporated to afford the desired product (56 mg). MS (ES+) 526 ($[MH]^+$), 350 ($[M-ArSO_2-]^+$), 548 ($[MNa]^+$).

Example 36 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexylmethanesulfinyl]-pyridine



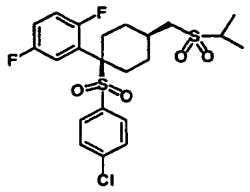
Prepared by oxidation of Example 34 by the method of Example 35 using one equivalent of 3-chloroperoxybenzoic acid.
MS (ES+) 510 ($[MH]^+$), 334 ($[M\text{-}ArSO_2\text{-}]^+$), 532 ($[MNa]^+$).

Example 37: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexylmethanesulfonyl]-pyridine-*N*-oxide



Prepared from Example 35 by treatment with urea hydrogen peroxide (2 equivalents) and trifluoroacetic anhydride (2 equivalents) in dichloromethane at 0°C. MS (ES+) 542 ($[MH]^+$), 366 ($[M\text{-}ArSO_2\text{-}]^+$).

Example 38: 1-(4-Chlorophenylsulfonyl)-1-(2,5-difluoro-phenyl)-4-[(2-propyl)sulfonylmethyl]-cyclohexane

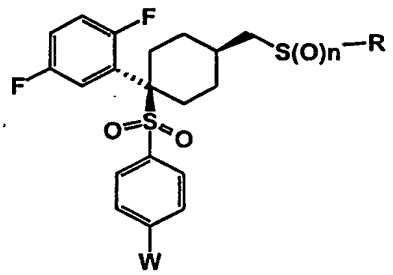


Intermediate E (150 mg, 0.29 mmol) was reacted with 2-propanethiol (30 μL, 0.32 mmol) by the method of Example 34. The resulting sulfide, in ethyl acetate (1 mL), was added to a stirring solution of sodium periodate (139 mg, 0.65 mmol) in a 1:2 solution of ethyl acetate:water (3 mL) and a catalytic amount of ruthenium (IV) oxide. The reaction mixture was

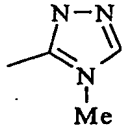
stirred at ambient temperature over 30 min., diluted with water, extracted with ethyl acetate, washed with brine, dried ($MgSO_4$) and evaporated to give a residue (135 mg) which was purified by preparative thin layer chromatography eluting with ethyl acetate:iso-hexane 1:3 to afford the desired product (39 mg). MS (ES+) 513 ($[MNa]^+$), 508 ($[MNH_4]^+$).

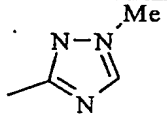
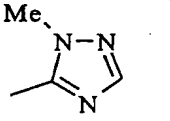
Examples 39-75, 78-90

In the following examples, Intermediate E or Intermediate M was reacted with the appropriate thiol as in Example 34 and (where necessary) oxidised as in Example 35 (Method A) or as in Example 38 (Method B), or as in Example 36 (Method C).



Ex. No.	n	Method	W	R	MS (ES+)/(ES-)
39	2	A	Cl	CH_2CF_3	548 ($[MNH_4]^+$), 553 ($[MNa]^+$)
40	2	A	Cl	n-propyl	508 ($[MNH_4]^+$)
41	2	A	Cl	isobutyl	522 ($[MNH_4]^+$), 527 ($[MNa]^+$)
42	2	A	Cl	4-pyridyl	350 ($[M\text{-}ArSO_2^-]^+$) 526 ($[MH]^+$), 548 ($[MNa]^+$)
43	2	A	Cl	2-pyrimidinyl	351 ($[M\text{-}ArSO_2^-]^+$) 527 ($[MH]^+$)
44	2	A	Cl	4-Me-2-thiazolyl	370 ($[M\text{-}ArSO_2^-]^+$) 546 ($[MH]^+$), 568 ($[MNa]^+$)

Ex. No.	n	Method	W	R	MS (ES+)/(ES-)
45	2	A	Cl	5-Me-[1,3,4]-thiadiazol-2-yl	371 ([M-$ArSO_2^-$]$^+$) 547 ([MH]$^+$), 569 ([MNa]$^+$)
46	2	A	Cl	2-Me-3-furyl	546 ([MNH_4]$^+$), 551 ([MNa]$^+$)
47	2	A	Cl	-CH_2COCH_3	527 ([MNa]$^+$)
48	2	A	Cl	2-furylmethyl	546 ([MNH_4]$^+$) 551 ([MNa]$^+$)
49	2	A	Cl	1-(2-thienyl)-ethyl	576 ([MNH_4]$^+$) 581 ([MNa]$^+$)
50	2	A	Cl	benzyl	556 ([MNH_4]$^+$) 561 ([MNa]$^+$)
51	2	A	Cl	cyclopentyl	517 ([MH]$^+$) 534 ([MNH_4]$^+$) 539 ([MNa]$^+$)
52	2	A	Cl	2-thiazolyl	356 ([M-$ArSO_2^-$]$^+$) 554 ([MNa]$^+$)
53	2	A	Cl	cyclohexyl	531 ([MH]$^+$) 548 ([MNH_4]$^+$) 553 ([MNa]$^+$)
54	2	A	Cl	2-thienyl	548 ([MNH_4]$^+$) 553 ([MNa]$^+$)
55	2	A	Cl	1-Me-1H-imidazol-2-yl	353 ([M-$ArSO_2^-$]$^+$) 529 ([MH]$^+$)
56	2	A	Cl		354 ([M-$ArSO_2^-$]$^+$) 530 ([MH]$^+$) 552 ([MNa]$^+$)
57	2	B	Cl	t-butyl	522 ([MNH_4]$^+$) 527 ([MNa]$^+$)
58	2	B	Cl	2-OH-ethyl	493 ([MH]$^+$)

Ex. No.	n	Method	W	R	MS (ES+)/(ES-)
					515 ([MNa]+)
59	2	B	Cl	1H-imidazol-2-yl	339 ([M-ArSO2-]+) 515 ([MH]+)
60	2	B	Cl	1-Me-1H-tetrazole-5-yl	335 ([M-ArSO2-]+) 531 ([MH]+), 553 ([MNa]+)
61	2	B	Cl	1H-[1,2,4]-triazol-3-yl	340 ([M-ArSO2-]+) 516 ([MH]+), 538 ([MNa]+)
62	1	C	Cl	1-Me-1H-tetrazole-5-yl	339 ([M-ArSO2-]+) 515 ([MH]+), 537 ([MNa]+).
63	2	A(a)	Cl	$CH_2C(Me)_2OH$	538 ([MNH4]+), 543 ([MNa]+)
64	2	A(b)	Cl	CH_2CH_2OMe	507 ([MH]+), 524 ([MNH4]+), 529 ([MNa]+).
65	2	A(c)	Cl	cyclopropyl	511 ([MNa]+)
66	2	A(d)	Cl		354 ([M-ArSO2-]+) 530 ([MH]+), 552 ([MNa]+)
67	2	A(d)	Cl		354 ([M-ArSO2-]+) 530 ([MH]+), 552 ([MNa]+).
68	2	A(c)	Cl	cyclobutyl	327 ([M-ArSO2-]+) 525 ([MNa]+).
69	0	-	Cl	CH_2CO_2Et	503 ([MH]+)
70	2	B	Cl	CH_2CO_2Et	nd
71	-	(e)	Cl	CH_2CO_2H	nd

Ex. No.	n	Method	W	R	MS (ES+)/(ES-)
72	0	-	Cl	$CH(Me)CO_2Et$	nd
73	2	B	Cl	$CH(Me)CO_2Et$	nd
74	2	B[(e)]	Cl	$CH(Me)CO_2H$	nd
75	2	B[(e)]	Cl	CH_2CO_2H	nd
78	0	-	CF_3	2-pyridyl	509 ($[MH-F]^+$)
79	0	-	CF_3	2-pyrimidinyl	529 ($[MH]^+$), 510 ($[MH-F]^+$)
80	2	A	CF_3	2-pyridyl	560 ($[MH]^+$)
81	2	A	CF_3	2-pyrimidinyl	561 ($[MH]^+$)
82	2	A	Cl	ethyl	477 ($[MH]^+$)
83	2	B	Cl	2-CF_3O-Ph	626 ($[MNH_4]^+$)
84	2	B	Cl	2-MeO-Ph	555 ($[MH]^+$)
85	2	B	Cl	2-F-Ph	565 ($[MNa]^+$)
86	2	B	Cl	4-F-Ph	565 ($[MNa]^+$)
87	2	B	Cl	2,4-di-F-Ph	583 ($[MNa]^+$)
88	2	B	Cl	2-OH-Ph	539 ($[M-H]^-$)
89	2	B	Cl	3-OH-Ph	539 ($[M-H]^-$)
90	2	B	Cl	4-OH-Ph	539 ($[M-H]^-$)

nd = not determined

(a) –2-mercaptoethyl acetate as thiol; treatment with MeMgBr in THF prior to oxidation.

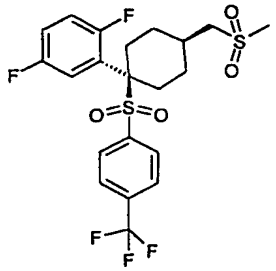
(b) – 2-mercaptoethanol as thiol; O-methylation (MeI, NaH, DMF) prior to oxidation.

(c) – thiol prepared by reaction of cycloalkylMgBr with sulfur then $LiAlH_4$ in THF.

(d) – via alkylation of Ex. 61 (MeI, K_2CO_3,DMF) then chromatographic separation of 1:1 mixture of positional isomers on silica; Ex. 66 the more polar isomer.

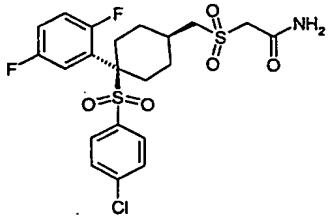
(e) – via hydrolysis of corresponding ester (LiOH in aqueous MeOH).

Example 76: 1-(4-Trifluoromethylphenylsulfonyl)-1-(2,5-difluoro-phenyl)-4-methanesulfonylmethyl-cyclohexane



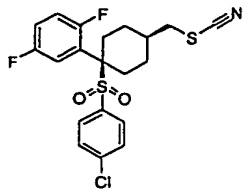
To Intermediate M (240 mg, 0.42 mmol) in ethanol (8 mL) was added sodium methanesulfinate (136 mg, 1.33 mmol). The reaction was refluxed for 18 h and after cooling was diluted with water, and extracted with ethyl acetate (x3). The organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica eluting with ethyl acetate to give the title compound (80 mg). MS (ES+) 519 ([MNa]$^+$).

Example 77: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexylmethanesulfonyl]-acetamide



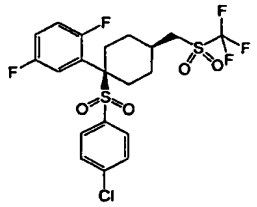
Prepared from Example 75 by treatment with pentafluorophenol and dicyclohexylcarbodiimide in ethyl acetate at0°C, then treatment with ammonia (2M in methanol) at 50°C in a sealed tube for 16 h.
MS (ES+) 506 ([MH]$^+$).

Example 91: [4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-methylisothiocyanate



To a stirred solution of Intermediate E (118 mg, 0.23 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium isothiocyanate (112 mg, 1.05 mmol) and the mixture warmed to 80°C for 18 hours. Upon cooling, ethyl acetate (20 mL) was added and the solution washed with water (3 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to leave a residue which was purified by flash column chromatography on silica, eluting with diethyl ether:iso-hexane 1:3, to afford the desired product (89 mg, 0.18 mmol.). MS (ES^+) 459 ($[MNH_4]^+$).

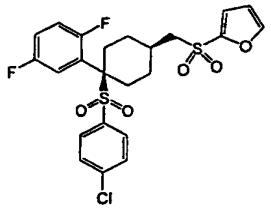
Example 92: {[4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-methyl}-trifluoromethyl sulfone



The product from Example 91 (80 mg, 0.18 mmol) in tetrahydrofuran (5 mL) at 0°C was treated with trimethyl(trifluoromethyl)silane (0.055 mL, 0.36 mmol) tetrabutylammonium fluoride (0.04 mL of a 1M solution in tetrahydrofuran, 0.04 mmol) and the mixture stirred for 5 minutes at 0°C then 3 hours at room temperature. Diethyl ether (20 mL) was added and the solution washed with water (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to leave a residue which was purified by flash column chromatography on silica eluting with diethyl ether:iso-hexane 1:3, to afford {[4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-methyl}-trifluoromethyl sulfide (49 mg,).

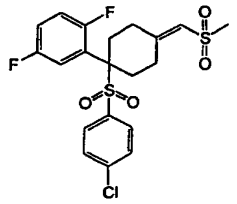
Of this, 47 mg (0.1 mmol) was oxidised to the sulfone by the method described in Example 38. Final purification was by flash column chromatography on silica eluting with diethyl ether:iso-hexane 1:2, to afford the desired product (38 mg). MS (ES^+) 534 ($[MNH_4]^+$).

Example 93: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexylmethanesulfonyl]-furan



To a solution of furan (0.043 mL, 0.67 mmol) in tetrahyrofuran (5 mL) at -40°C under nitrogen was added n-butyl lithium (0.41 mL of a 1.6M solution in hexanes, 0.66 mmol) and the reaction allowed to attain room temperature over 1 hour. Upon recooling to 0°C, sulfur (6 mg, 0.19 mmol) was added and the reaction stirred for 30 minutes at 0°C before a solution of Intermediate E (100 mg, 0.20 mmol) in ethanol (5 mL) was added. The mixture was then warmed to 60°C for 75 minutes, cooled, quenched by the addition of a saturated aqueous solution of ammonium chloride (20 mL), then extracted into ethyl acetate (2 x 30 mL). The combined organics were washed with water (2 x 10 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to leave a residue of the crude furan thioether (102 mg). This was oxidised to the sulfone by the method described in Example 38. Final purification was by flash column chromatography on silica, eluting with diethyl ether:iso-hexane 1:1, to afford the desired product (26 mg). MS (ES^+) 532 ($[MNH_4]^+$).

Example 94: 1-(4-Chlorophenylsulfonyl)-1-(2,5-difluoro-phenyl)-4-methanesulfonylmethylene-cyclohexane



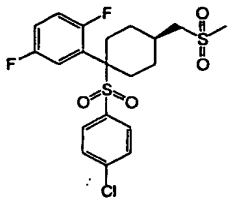
To a stirred solution of diisopropylamine (0.72 mL, 5.2 mmol) in tetrahydrofuran (40 mL) at –78°C was added dropwise a solution of n-butyl lithium (1.6M in hexanes, 3.2 mL, 5.1 mmol). The mixture was allowed to warm briefly to room temperature then recooled to –78°C and dimethyl sulfone (470 mg, 5.1 mmol) in tetrahydrofuran (10 mL) added dropwise. After stirring for 20 minutes at –78°C, Intermediate A (640 mg, 1.67 mmol) in tetrahydrofuran (10 mL) was added and stirring continued for a further 1 hour. The reaction was quenched by the addition of saturated aqueous ammonium chloride (50 mL), allowed to warm to room temperature then extracted into ethyl acetate (2 x 50 mL). The combined organics were washed with 2N aqueous hydrochloric acid (2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated to leave a residue which was purified by flash column chromatography on silica, eluting with ethyl acetate:iso-hexane 1:1, to afford 4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-1-methanesulfonylmethyl-cyclohexanol (630 mg).
MS (ES^+) 496 ($[MNH_4]^+$).

The alcohol from the foregoing step (420 mg, 0.88 mmol) in dichloromethane (20 mL) was cooled to 0°C under nitrogen and triethylamine (0.25 mL, 1.7 mmol) and methane sulfonyl chloride (0.1 mL, 1.3 mmol) were added. The reaction was stirred for 1 hour at 0°C then further triethylamine (0.5 mL, 3.4 mmol) and methane sulfonyl chloride (0.21 mL, 2.7 mmol) added. After a further 30 minutes, the solution was washed with 2N aqueous hydrochloric acid (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$), evaporated and the residue taken up in tetrahydrofuran (20 mL). 1,8-diazabicyclo[5.4.0]undec-7-ene (0.26 mL, 1.7 mmol) was

added and the mixture stirred for 5 minutes. Ethyl acetate (30 mL) was added, the solution washed with 1N aqueous sodium hydroxide (20 mL), and the aqueous layer extracted with further ethyl acetate (10 mL). The combined organic layers were washed with 2N aqueous hydrochloric acid (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to leave a residue which was purified by flash column chromatography on silica eluting with ethyl acetate:iso-hexane 1:1, to afford the desired product (196 mg).

MS (ES^+) 478 ($[MNH_4]^+$).

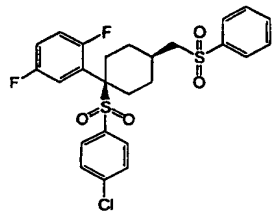
Example 95: 1-(4-Chlorophenylsulfonyl)-1-(2,5-difluoro-phenyl)-4-methanesulfonylmethyl-cyclohexane



The product of Example 94 (150 mg, 0.32 mmol) in tetrahydrofuran (20 mL) at –40°C was treated dropwise with L-Selectride™ (1M solution in tetrahydrofuran, 0.5 mL, 0.5 mmol). The reaction was stirred at –40°C for 90 minutes, then quenched by the addition of ethanol (4 drops) then water (10 mL). The mixture was extracted into ethyl acetate (2 x 50 mL) and the combined organics washed with brine (50 mL), dried ($MgSO_4$) and evaporated to leave a residue which was purified by flash column chromatography on silica eluting with diethyl ether:dichloromethane:iso-hexane 1:2:1, to afford the desired product (107 mg).

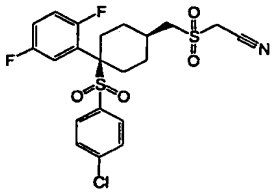
MS (ES^+) 480 ($[MNH_4]^+$).

Example 96: 1-(4-Chlorophenylsulfonyl)-1-(2,5-difluoro-phenyl)-4-phenylsulfonylmethyl-cyclohexane



Prepared as in Example 76 using Intermediate E, sodium phenylsulfinate and DMF as solvent. MS (ES+) 542 ($[MNH_4]^+$).

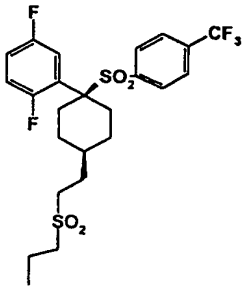
Example 97: 1-(4-Chlorophenylsulfonyl)-1-(2,5-difluoro-phenyl)-4-[(cyanomethyl)sulfonylmethyl]-cyclohexane



To a stirred solution of Intermediate I (120 mg, 0.29 mmol) in acetonitrile (5 mL) was added potassium carbonate (41 mg, 0.30 mmol) and a solution of chloroacetonitrile (0.04 mL, 0.64 mmol) in acetonitrile (10 mL) and the reaction warmed to 50°C for 2 hours. Upon cooling, the mixture was filtered and the filtrate evaporated. The residue was taken up in ethyl acetate (3 mL) and oxidised to the sulphone by the method described in Example 83. Finalpurification was by flash column chromatography on silica eluting with diethyl ether:iso-hexane 1:1, to afford the desired product (51 mg).

MS (ES^-) 486 ($[M-H]^-$).

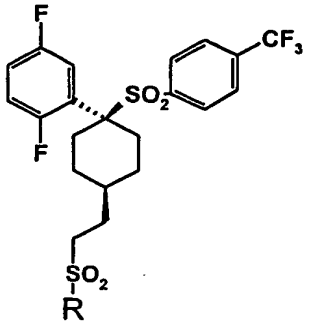
Example 98: 1-(2,5-Difluoro-phenyl)-1-(4-trifluoromethylphenylsulfonyl)-4-propylsulfonylethyl-cyclohexane



A stirred solution of Intermediate P (0.115 g, 0.22 mmol), 1-propanethiol (0.021 mL, 0.22 mmol) and powdered potassium hydroxide (0.015 mg, 0.26 mmol) in ethanol (5 mL) was heated at reflux for 45 minutes, then evaporated. The residue was dissolved in diethyl ether (25 mL), washed with brine (20 mL), dried over magnesium sulfate and evaporated to dryness.

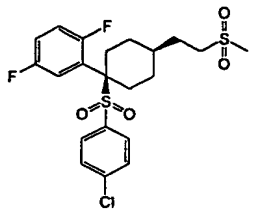
The resulting crude thioether in dichloromethane (10 mL) was oxidised as described in Example 35. MS (ES+) 539 ([MH]+).

Examples 99 to 102 were prepared from Intermediate P by the method of Example 98 using the appropriate thiol.



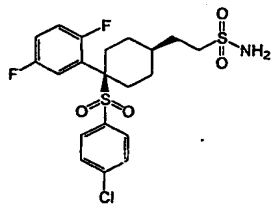
Example	R	MS (ES+)
99	Isopropyl	539 ([MH]+)
100	2-pyridyl	574 ([MH]+)
101	2-pyrimidyl	575 ([MH]+)
102	2-chlorophenyl	629 ([MNa]+)

Example 103: 1-(4-Chlorophenylsulfonyl)-1-(2,5-difluoro-phenyl)-4-[2-(methylsulfonyl)ethyl]-cyclohexane



Prepared from Intermediate F and sodium methylsulfinate by the method of Example 96. MS (ES+) 499 ([MNa]+).

Example 104: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-ethanesulfonic acid amide

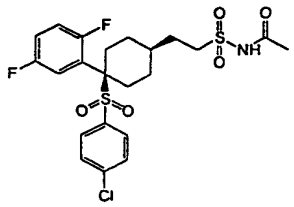


Intermediate D (5.09 g, 12.3 mmol) was converted to the mesylate following the procedure of Intermediate P.

The foregoing mesylate (1.18 g, 2.4 mmol) was converted to the thiol following the procedure of Intermediate I.

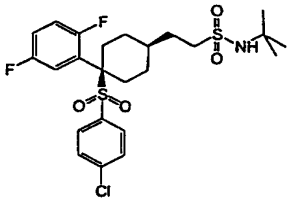
This product was converted to the sulfonyl chloride by the procedure of Intermediate Q, which was dissolved in dichloromethane (10 ml) and ammonia gas bubbled through for 5 minutes. The resulting cloudy solution was stirred at ambient temperature for 15 minutes then evaporated and taken up in ethyl acetate (20 mL), washed with water (20 ml) and brine (20 mL), dried ($MgSO_4$) and evaporated to leave a residue which was triturated with diethyl ether to afford the desired product (51 mg) MS (ES+) 500 ([MNa]+).

Example 105: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-ethanesulfonic acid acetyl-amide



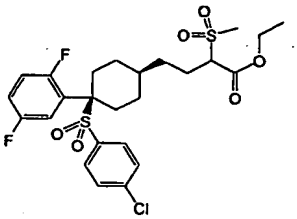
Prepared from Example 104 by coupling with acetic acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and dimethylaminopyridine in dichloromethane. MS (ES+) 542 ([MNa]+).

Example 106: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-ethanesulfonic acid tert-butylamide



Prepared by coupling [4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-ethanesulfonyl chloride (see Example 104) with *tert*-butylamine in dichloromethane (5mL). MS (ES+) 556 ([MNa]+).

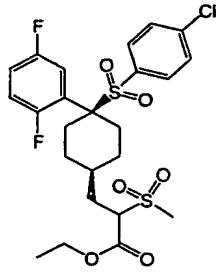
Example 107: 4-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-2-methanesulfonyl-butyric acid ethyl ester



Ethyl methanesulfonylacetate (0.285 mL, 2.15 mmol) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil, 94 mg, 2.37 mmol) in *N,N*-dimethylformamide (7.0 mL) at 0°C. The reaction was stirred at 0°C for one hour, before the addition of Intermediate F (1.13 g, 2.15 mmol) in *N,N*-dimethylformamide (2 mL). The reaction was stirred

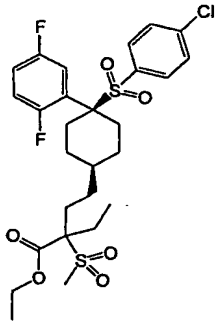
at 0°C for a further 2 hours, then for a further12 hours, warming gradually. The reaction was partitioned between diethyl ether (150 mL) and 1M aqueous hydrochloric acid (150 mL), the phases separated and the aqueous layer washed with diethyl ether. The combined organic layers were washed with 1N aqueous sodium hydrogencarbonate and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed using a Biotage™ 40S column, eluting with 70/30 iso-hexane/acetone to give the title compound (769 mg). MS (ES-) 561 ([M-H]-).

Example 108: 3-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-2-methanesulfonyl-propionic acid ethyl ester



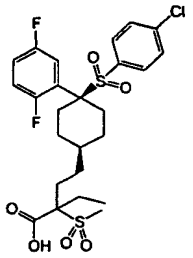
Prepared by the procedure of Example 107 using Intermediate E.
MS (ES-) 547 ([M-H]-).

Example 109: 4-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-2-ethyl-2-methanesulfonyl-butyric acid ethyl ester



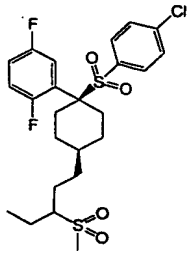
Prepared from Example 107 by alkylation with ethyl trifluoromethanesulfonate using NaH in dimethylformamide.
MS (ES-) 589 ([M-H]-).

Example 110: 4-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-2-ethyl-2-methanesulfonyl-butyric acid



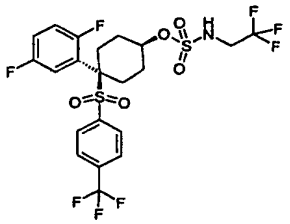
The product of Example 109 was hydrolyzed by heating to 50°C with LiOH in aqueous THF, followed by extractive work-up.
MS (ES-) 561 ([M-H]-).

Example 111: 1-(4-Chlorophenylsulfonyl)-1-(2,5-difluoro-phenyl)-4-[(3-sulfonylmethyl)pentyl]-cyclohexane



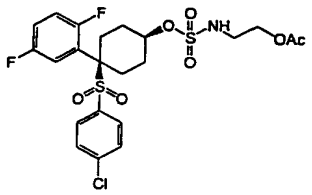
Prepared from Example 110 by refluxing with excess sodium chloride in 58% aqueous dimethylsulfoxide for 26 hours. MS (ES+) 519 ([MH]+).

Example 112: (2,2,2-Trifluoro-ethyl)-sulfamic acid 4-(2,5-difluoro-phenyl)-4-(4-trifluoromethyl-benzenesulfonyl)- cyclohexyl ester



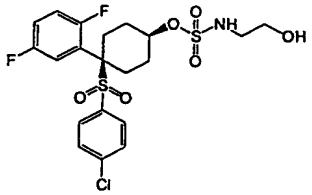
Prepared from Intermediate O by treatment with trifluoroethyl sulfamoyl chloride and triethylamine in dry dichloromethane under nitrogen.

Example 113: acetic acid 2-[4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyloxysulfonylamino]-ethyl ester



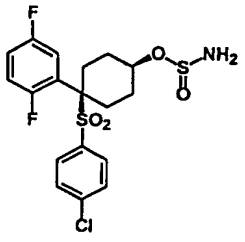
Prepared by treatment of Intermediate G by treatment with 2-acetoxyethylsulfamoyl chloride and triethylamine in *N,N*-dimethylacetamide at 60°C. MS (ES+) 574 ([MNa]+).
The sulfamoyl chloride was obtained from reaction of 2-aminoethyl acetate hydrochloride with sulfuryl chloride in acetonitrile.

Example 114: (2-Hydroxy-ethyl)-sulfamic acid 4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl ester



Prepared from Example 113 by hydrolysis with LiOH in aqueous tetrahydrofuran. MS (ES+) 510 ([MH]+).

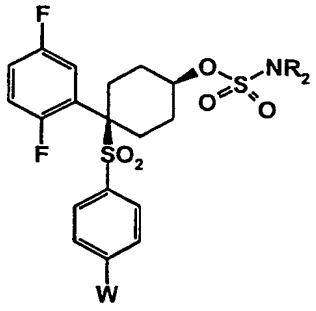
Example 115: Sulfinamic acid 4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl ester



Prepared from Intermediate G by treatment with thionyl chloride and pyridine in dichloromethane at –78°C and subsequently with ammonia gas, also at –78°C. was bubbled through keeping the temperature at –

78°C. After 20 minutes, the reaction vessel was sealed and left to stir for 19 hours slowly warming to room temperature. MS (ES-) 448 ([M-H]-).

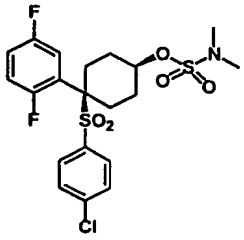
Examples 116-120:



Prepared from Intermediate G or Intermediate O by the procedure of Example 113, carried out at ambient temperature.

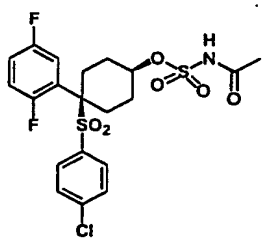
Example	W	NR_2	MS (ES+)/(ES-)
116	Cl	NH_2	488 ([MNa]+).
117	CF_3	NH_2	522 ([MNa]+)
118	Cl	NHEt	516 ([MNa]+)
119	Cl	$NHCH_2CF_3$	546 ([MH]-).
120	Cl	NH^tBu	520 ([MH]-)

Example 121: Dimethyl-sulfamic acid 4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl ester



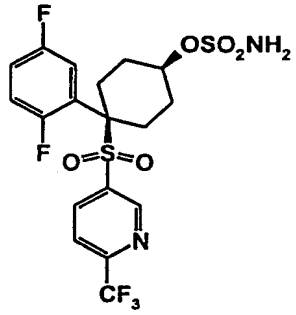
Prepared from Example 116 by alkylation with excess MeI in tetrahydrofuran cooled to –78°C using lithium bis(trimethylsilyl)amide (1M solution in tetrahydrofuran) as base. MS (ES+) 516 ([MNa]+).

Example 122: Acetyl-sulfamic acid 4-(4-chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl ester



Prepared from Example 116 by treatment with acetic anhydride in pyridine at room temperature. MS (ES+) 530 ([MNa]+).

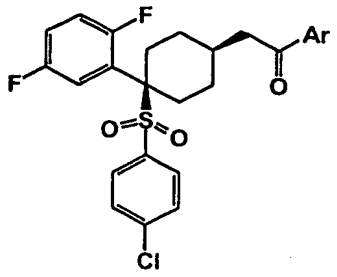
Example 123: Sulfamic acid 4-(2,5-difluoro-phenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexyl ester



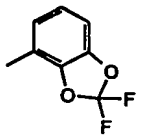
4-(2,5-Difluoro-phenyl)-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-cyclohexanone (Intermediate T, steps 1-4) was reduced to the *cis*-cyclohexanol using L-Selectride™ (1M in tetrahydrofuran) as described for Inermediate G

This alcohol was treated with sulfamoyl chloride as in Examples 116-120 to give the desired product as a white solid. MS (ES+) 501 ([MH]+).

Examples 124-127, 129, 147-150:



The following were prepared from Intermediate H by reaction with ArMgBr in THF at 0°C.

Example	Ar	MS (ES+)
124		393 ([M-$ArSO_2^-$]$^+$), 591 ([MNa]$^+$).
125	3-allyloxyphenyl	567 ([MNa]$^+$).
126[a]	2-(MeO_2C-CH_2O)-Ph	401 ([M-$ArSO_2^-$]$^+$), 599 ([MNa]$^+$)
127[b]	2-(HO_2C-CH_2O)-Ph	563 ([MH]$^+$), 387 ([M-$ArSO_2^-$]$^+$).
129[a],[b]	2-(HO_2C-$(CH_2)_3O$)-Ph	nd
147	3-(1,3-dioxolan-2-yl)phenyl	583 ([MNa]$^+$)
148[c]	3-CHO-Ph	539 ([MNa]$^+$)
149[d]	3-CO_2H-Ph	555 ([MNa]$^+$)
150[c]	2-CHO-Ph	517 ([MH]$^+$)
151[d]	2-CO_2H-Ph	555 ([MNa]$^+$)

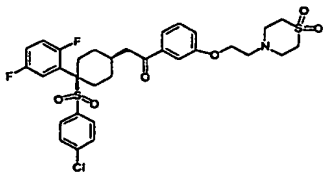
(a) – starting from the 2-allyloxy derivative. Cleavage to the phenol occurred in situ, and this was alkylated with the relevant chloroester.

(b) – hydrolysis of corresponding ester as final step.

(c) – cleavage of the corresponding 1,3-dioxolan as final step (pyridinium p-toluenesulfonate in aqueous acetone).

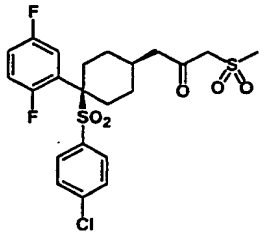
(d) – oxidation of corresponding aldehyde as final step (using Dess-Martin periodinane).

Example 128: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-1-{3-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-phenyl}-ethanone



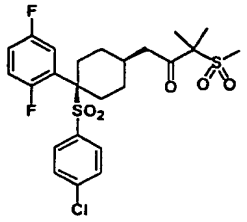
The product from Example 125 was treated with ozone in 1:5 methanol:dichloromethane under nitrogen at -78°C to form the corresponding aldehyde. This aldehyde and 1,1-dioxothiomorpholine in methanol/dichloromethane was treated with triethylamine, methanolic HCl and sodium cyanoborohydride to afford the desired product.
MS (ES+) 666 ($[MH]^+$), 490 ($[M-ArSO_2^-]^+$).

Example 130: 1-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-3-methanesulfonyl-propan-2-one



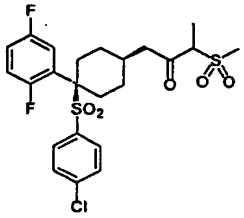
Dimethyl sulfone was reacted with 1 equivalent of lithium diisopropylamide in tetrahydrofuran at -78°C, and the resulting carbanion was reacted *in situ* with Intermediate B at -78°C for 30 minutes then at ambient temperature for 1 hour to yield the desired product.
MS (ES+) 505 ($[MH]^+$).

Example 131: 1-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-3-methanesulfonyl-3-methyl-butan-2-one



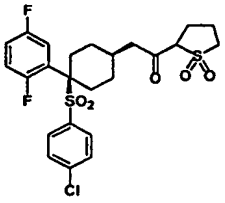
Prepared from Example 131 by alkylation with excess MeI in 1,2-dimethoxyethane at room temperature using sodium hydride as base. (MS (ES+) 555 ([MNa]+).

Example 132: 1-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-3-methanesulfonyl-butan-2-one



The product from Example 130 was methylated as described in Example 131, using one equivalent each of MeI and NaH. MS (ES+) 541 ([MNa]+).

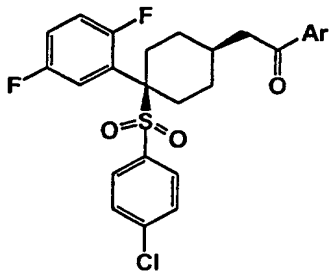
Example 133: 2-[4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-1-(1,1-dioxo-tetrahydrothiophen-2-yl)-ethanone

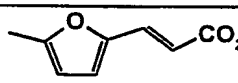
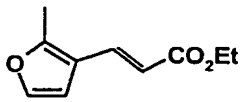
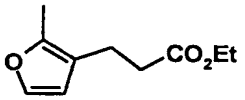
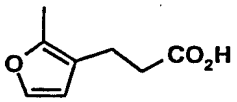
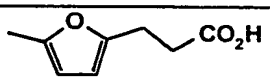
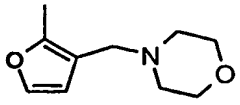


Prepared by the procedure of Example 130 using tetramethyl sulfone. MS (ES+) 553 ([MNa]+).

Examples 134-146

The following were prepared by reaction of Intermediate H with ArLi in diethyl ether or THF at -78°C:



Example	Ar	MS (ES+)
134[a]	2-pyridyl–N-oxide	330 ([M-$ArSO_2^-$]$^+$), 506 ([MH]$^+$), 528 ([MNa]$^+$)
135	5-$HOCH_2$-furan-2-yl	531 ([MNa]$^+$)
136[b]	5-HCO-furan-2-yl	507 ([MH]$^+$)
137[c]	5-HOOC-furan-2-yl	523 ([MH]$^+$)
138[d]		577 ([MH]$^+$).
139	3-$HOCH_2$-furan-2-yl	509 ([MH]$^+$).
140[b]	3-HCO-furan-2-yl	529 ([MNa]$^+$)
141[c]	3-HOOC-furan-2-yl	523 ([MH]$^+$)
142[d]		577 ([MH]$^+$)
143[e]		579 ([MH]$^+$)
144[f]		551 ([MH]$^+$)
145[e],[f]		551 ([MH]$^+$)
146[g]		578 ([MH]$^+$).

(a) – oxidation as final step (urea hydrogen peroxide, trifluoroacetic anhydride in dichloromethane).

(b) – via oxidation of the corresponding hydroxymethyl compound (Dess-Martin periodinane in dichloromethane).

(c) – via oxidation of the corresponding aldehyde (sulfamic acid and sodium chlorite in dichloromethane/water).

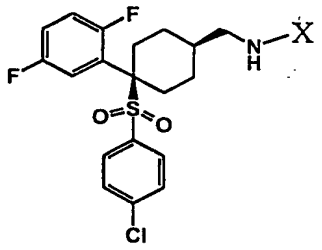
(d) – via condensation of the corresponding aldehyde with $(EtO)_2POCH_2CO_2Et$.

(e) – via hydrogenation of the corresponding olefin (over Rh/C catalyst).

(f) – via hydrolysis of the corresponding ester (LiOH in aqueous THF).

(g) – via reaction of the corresponding aldehyde with morpholine and sodium cyanoborohydride in MeOH/HCl.

Example 152-155,157,161,162

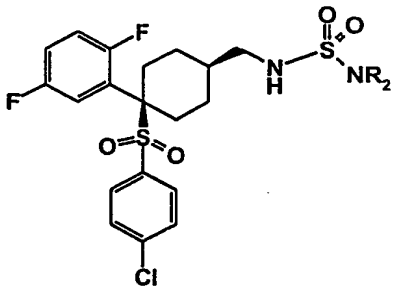


The following were prepared from Intermediate J by reaction with the appropriate acid chloride or anhydride and triethylamine in dichloromethane under nitrogen at ambient or reduced temperature (method A) or by coupling with the appropriate carboxylic acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, hydroxybenzotriazole and triethylamine in DMF at ambient temperature (method B), or by refluxing in dioxan with sulfamide (method C).

Example	X	Method	MS (ES+)
152	acetyl	A	442 ([MH]+)
153	-SO_2Me	A	
154	-CO_2Me	A	458 ([MH]+) 282 ([M-$ArSO_2^-$]+)

155	-SO_2CF_3	A	
157	-SO_2NH_2	C	
161	-$COCH_2CF_3$	B	510 ([MH]+)
162	-$COCH(OH)CF_3$	B	526 ([MH]+)

Example 156, 158-160

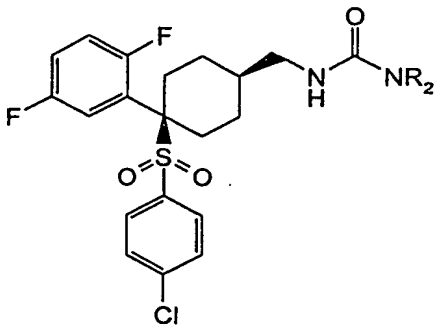


The following were prepared from Intermediate J by reaction with catechol sulphate in dry tetrahydrofuran under nitrogen at 0°C, and treatment of the resulting 2-hydroxyphenyl sulfamate with the appropriate amine R_2NH at 80°C in dioxan.

Example	NR_2	MS (ES+)
156	pyrrolidine	533 ([MH]+).
158	NHEt	507 ([MH]+), 529 ([MNa]+).
159	(L)-proline Me ester	591 ([MH]+)
160[a]	(L)-proline	577 ([MH]+)

(a) – by hydrolysis of Example 159

Examples 163 -165

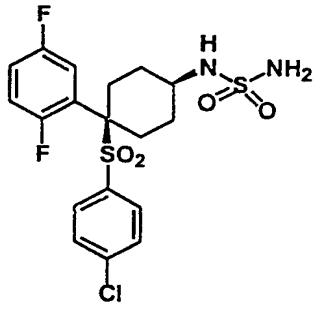


The following were prepared from Intermediate C by reaction with triethylamine and diphenylphosphoryl azide in toluene at 110°C for 3 hours, followed by treatment with the appropriate amine R_2NH for a further 18 hours at ambient temperature.

MS (ES+)

Example	NR_2	MS (ES+)
163	NHMe	457 ([MH]+)
164	NH_2	443 ([MH]+)
165	NMe_2	471 ([MH]+)

Example 167: [4-(4-Chloro-benzenesulfonyl)-4-(2,5-difluoro-phenyl)-cyclohexyl]-sulfamic amide

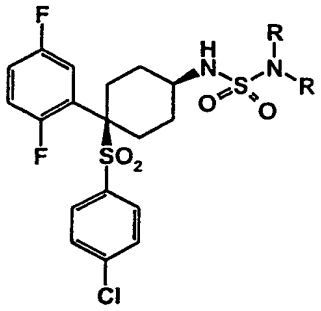


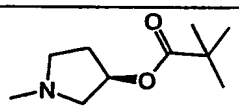
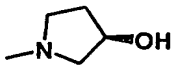
Intermediate R (100 mg, 0.26 mmol in dioxane (4 ml) was treated with sulfamide (125 mg, 1.30 mmol) and heated to reflux for 1 hour, then cooled to room temperature, diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$) and evaporated. Trituration of the residue in ether afforded the desired product (50 mg, 42% yield). m/z = 465, 467 [MH]+

Examples 168-184:

The following were prepared from Intermediate R by treatment with the appropriate sulfamoyl chloride and triethylamine in a mixture of dichloromethane and dimethylacetamide (3:1) (Method A); or by treatment with the appropriate sulfamoyl chloride and Hünig's base in acetonitrile at 80°C (Method B)

The relevant sulfamoyl chlorides were prepared by published methods (DE 3429048; FR 2739858; *J.Org.Chem.*, 41, 4029-9, 1976; *J.Heterocyclic Chem.*,2000, 773) or adaptations thereof.



Example	Method	NR_2	MS M/Z (ES^-)
168	A	NMe_2	491, 493
169	A	NHEt	491, 493
170	A	$NHCH_2CF_3$	545, 547
171	A	NH^tBu	519, 521
172	A	pyrrolidin-1-yl	517, 519
173	A	azetidin-1-yl	503, 505
174	A	3,3-difluoroazetidin-1-yl	539, 541
175	A	4-trifluoromethylpiperidin-1-yl	599, 601
176	B	morpholin-1-yl	533, 535
177	B		619, 621
178	(a)		533, 535
179	(b)	3-oxo-pyrrolidin-1-yl	533, 535
180	(c)	3-OH-3-Me-pyrrolidin-1-yl	571, 573
181	B,(a)	3-hydroxy-azetidin-1-yl	521, 523
182	(b)	3-oxo-azetidin-1-yl	-
183	(c)	3-OH-3-Me-azetidin-1-yl	535
184	(d)	3-Me_2N-azetidin-1-yl	548

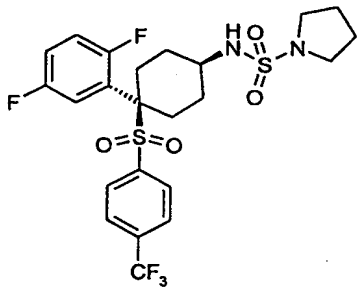
(a) – treatment of corresponding pivalate with DIBAL-H in toluene at ambient temp.

(b) – oxidation of corresponding alcohol with Dess-Martin periodinane I dichloromethane at ambient temperature.

(c) – reaction of corresponding ketone with MeMgBr in THF at 0°C.

(d) – reaction of Ex. 182 with Me_2NH and sodium cyanoborohydride in MeOH at ambient temperature.

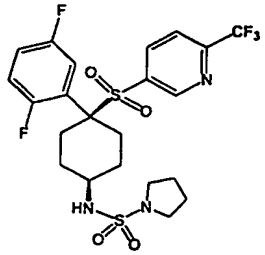
Example 185: Pyrrolidine-1-sulfonic acid [4-(2,5-difluoro-phenyl)-4-(4-trifluoromethyl-benzenesulfonyl)-cyclohexyl]-amide



Sulfuryl chloride (236 µl, 2.9 mmol) in toluene (2 ml) was cooled to –30°C and pyrrolidine (242 µl, 29 mmol) added dropwise over 10 min. The reaction was stirred for 1.5 h at –30°C, diluted with toluene, washed with water, aqueous HCl (2 M) and brine, dried ($MgSO_4$), filtered and evaporated to give an oil. This was dissolved in dichloromethane (1 ml) and added to a solution of Intermediate S (120 mg, 0.29 mmol) in dichloromethane (2 ml) at 0°C and the reaction allowed to warm to room temperature and stirred for 18 h. The mixture was diluted with dichloromethane, washed with water, brine, dried ($MgSO_4$) filtered and evaporated. The residue was purified by flash chromatography eluting with *iso*-hexane/ethyl acetate (1:1) to give a white solid (62 mg).

MS [MH^+] 553

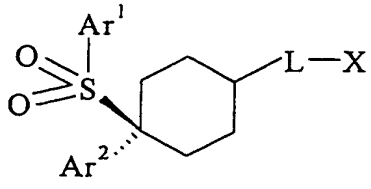
Example 186: Pyrrolidine-1-sulfonic acid [4-(2,5-difluoro-phenyl)-4-(6-trifluoromethyl-pyridyl-3-sulfonyl)-cyclohexyl]-amide



Prepared by the procedure described for Example 185, using Intermediate T. m/z = 554 (MH^+)

CLAIMS:

1. A compound of formula I:



I

wherein

X represents SCN, SR^1, $S(O)R^1$, $(CR^aR^b)_mSO_2R^1$, $SO_2N(R^2)_2$, SO_2NHCOR^1, $SO_2NHN(R^2)_2$, $OSO_2N(R^2)_2$, $OS(O)N(R^2)_2$, OSO_2NHCOR^1, COR^4, $NHCOR^1$, $NHCO_2R^1$, $NHCON(R^2)_2$, $NHSO_2R^1$ or $NHSO_2N(R^2)_2$;

m is 0 or 1

R^a represents H or C_{1-4}alkyl;

R^b represents H, C_{1-4}alkyl, CO_2H, C_{1-4}alkoxycarbonyl or C_{1-4}alkylsulphonyl; or R^b may combine with R^1 to form a 5- or 6-membered ring;

L represents a bond, =CH- or $-(CHR^a)_n-$; with the proviso that L does not represent a bond when X represents $NHCOR^1$, $NHCO_2R^1$ or $NHSO_2R^1$; and with the proviso that if L represents =CH-, X represents SO_2R^1 or COR^4;

n is 1, 2 or 3;

R^1 represents CF_3 or C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-9}cycloalkyl or C_{3-6}cycloalkylC_{1-6}alkyl, any of which may bear up to 2 substituents selected from halogen, CN, CF_3, OR^3, COR^3, CO_2R^3, $OCOR^{3a}$, SO_2R^{3a}, $N(R^5)_2$, and $CON(R^5)_2$,

or R^1 represents aryl, arylC_{1-6}alkyl, C-heterocyclyl or C-heterocyclylC_{1-6}alkyl;

or R^1 may combine with R^b to form a 5- or 6-membered ring;

each R^2 independently represents H, C_{1-6}alkoxy, or C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-9}cycloalkyl or C_{3-6}cycloalkylC_{1-6}alkyl, any of which may bear

up to 2 substituents selected from halogen, CN, CF_3, OR^3, COR^3, CO_2R^3, $OCOR^{3a}$, and $CON(R^5)_2$; or aryl, arylC_{1-6}alkyl, C-heterocyclyl or C-heterocyclylC_{1-6}alkyl;

or two R^2 groups together with a nitrogen atom to which they are mutually attached complete an N-heterocyclyl group;

R^3 represents H, C_{1-4}alkyl, phenyl or heteroaryl;

R^{3a} represents C_{1-4}alkyl, phenyl or heteroaryl;

R^4 represents $(CR^aR^b)SO_2R^1$, pyridine N-oxide, or phenyl or heteroaryl which bear a substituent selected from CO_2H, methylenedioxy, difluoromethylenedioxy, COR^3, C-heterocyclyl, C_{1-4}alkylsulphonyl and substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, OR^3, CO_2R^3, $OCOR^{3a}$, $N(R^5)_2$ and $CON(R^5)_2$;

R^5 represents H or C_{1-4}alkyl, or two R^5 groups together with a nitrogen atom to which they are mutually attached complete an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine or thiomorpholine-1,1-dioxide ring;

Ar^1 and Ar^2 independently represent phenyl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, CHF_2, OH, OCF_3, CHO, CH=NOH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, C_{2-6}acyl, C_{2-6}alkenyl and C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

"aryl" at every occurrence thereof refers to phenyl or heteroaryl which optionally bear up to 3 substituents selected from halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^{3a}$, $N(R^5)_2$, $CON(R^5)_2$ and optionally-substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, phenyl, OR^3, CO_2R^3, $OCOR^{3a}$, $N(R^5)_2$ and $CON(R^5)_2$; and

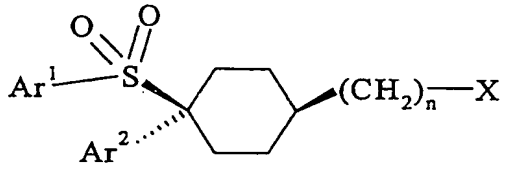
"C-heterocyclyl" and "N-heterocyclyl" at every occurrence thereof refer respectively to a heterocyclic ring system bonded through carbon or

nitrogen, said ring system being non-aromatic and comprising up to 10 atoms, at least one of which is O, N or S, and optionally bearing up to 3 substituents selected from oxo, halogen, CN, NO_2, CF_3, OCF_3, OR^3, COR^3, CO_2R^3, $OCOR^{3a}$, OSO_2R^{3a}, $N(R^5)_2$, $CON(R^5)_2$ and optionally-substituted phenyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkenyloxy wherein the substituent is selected from halogen, CN, CF_3, OR^3, CO_2R^3, $OCOR^{3a}$, $N(R^5)_2$ and $CON(R^5)_2$;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X is selected from SR^1, $(CR^aR^b)_mSO_2R^1$, $SO_2N(R^2)_2$, $OSO_2N(R^2)_2$, COR^4, $NHCOR^1$, $NHCO_2R^1$, $NHCON(R^2)_2$, $NHSO_2R^1$ and $NHSO_2N(R^2)_2$.

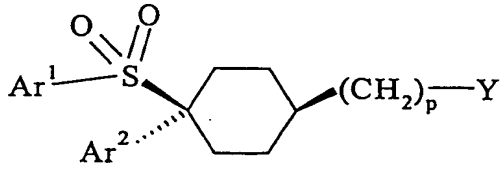
3. A compound according to claim 1 which is in accordance with formula II:



II

or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 which is in accordance with formula II:



III

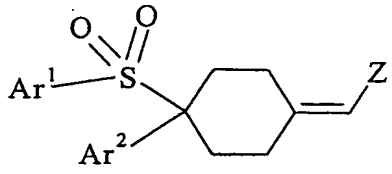
wherein p is 0, 1, 2 or 3;

Y is SCN, SR^1, $S(O)R^1$, $(CR^aR^b)_mSO_2R^1$, $SO_2N(R^2)_2$, SO_2NHCOR^1, $SO_2NHN(R^2)_2$, $OSO_2N(R^2)_2$, $OS(O)N(R^2)_2$, OSO_2NHCOR^1, COR^4, $NHCON(R^2)_2$ or $NHSO_2N(R^2)_2$;

and m, R^a, R^b, R^1, R^2, R^4, Ar^1 and Ar^2 are as defined in claim 1;

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1 which is in accordance with formula IV:



IV

wherein Z represents SO_2R^1 or COR^4;

and R^1, R^4, Ar^1 and Ar^2 are as defined in claim 1;

or a pharmaceutically acceptable salt thereof.

6. A compound according to any previous claim wherein Ar^1 is 4-chlorophenyl or 4-trifluoromethylphenyl or 6-(trifluoromethyl)-3-pyridyl and Ar^2 is 2,5-difluorophenyl.

7. A pharmaceutical composition comprising a compound according to any previous claim and a pharmaceutically acceptable carrier.

8. A compound according to any of claims 1-6 for use in a method of treatment of the human body.

9. The use of a compound according to any of claims 1-6 in the manufacture of a medicament for treating or preventing Alzheimer's disease.

10. A method of treatment of a subject suffering from or prone to a condition associated with the deposition of β-amyloid which comprises administering to that subject an effective amount of a compound according to any of claims 1-6.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 03/04102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C317/14 C07C317/18 C07C317/20 C07C317/22 C07C317/24
C07C317/44 C07C331/04 C07D205/04 C07D205/06 C07D207/08
C07D207/10 C07D207/16 C07D211/38 C07D213/70 C07D213/71
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 70677 A (MERCK FROSST CANADA) 27 September 2001 (2001-09-27) cited in the application the whole document	1,6-10

☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2004	20/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	English, R

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INTERNATIONAL SEARCH REPORT

Inten ·al Application No
PCT/GB 03/04102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/89 C07D233/84 C07D239/38 C07D249/08 C07D257/04
C07D277/36 C07D295/08 C07D295/26 C07D307/38 C07D307/64
C07D317/26 C07D317/48 C07D333/18 C07D333/48 C07D491/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2004	

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European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB 03/04102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/10 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2004	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...ational application No.
PCT/GB 03/04102

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[] The additional search fees were accompanied by the applicant's protest.

[] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]al Application No
PCT/GB 03/04102

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0170677 A	27-09-2001	AU 4086101 A	03-10-2001
		CA 2404125 A1	27-09-2001
		EP 1268412 A1	02-01-2003
		WO 0170677 A1	27-09-2001
		JP 2003528076 T	24-09-2003
		AU 1074702 A	15-05-2002
		CA 2427206 A1	10-05-2002
		EP 1334085 A1	13-08-2003
		WO 0236555 A1	10-05-2002

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